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TETRAHEDRON LETTERS, vol. 26, no. 16, 1985, pages 2013-2016, GB; T.W. HART, "Some observations concerning the S-nitroso and S-phenylsulphonyl derivatives of L-cysteine and glutathione"
JOURNAL OF THE CHEMICAL SOCIETY - PERKIN TRANSACTIONS I, 1979, pages 1969-1974; R. BONNETT et al, "Nitrosation and nitrosylation of haemoproteins and related compounds. Part 2. The reaction of nitrous acid with the side chains of alpha-acyl-amino-acid esters"

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ANGEWANDTE CHEMIE, vol. 87, no. 10, 1975, pages 372-378, Weinheim, DE; W. M. WEIGERT et al, "D-Penicillamin - Herstellung und Eigenschaften"
CHEMICAL ABSTRACTS, vol. 95, no. 15, 12 October 1981, page 62, abstract no. 126235k, Columbus, Ohio, US; D. ZIEBARTH et al, "Nitrosation of orally administered drugs under simulated stomach conditions"

(73) Proprietor : **Takeda Chemical Industries, Ltd.**
1-1, Doshomachi 4-chome
Chuo-ku, OSAKA (JP)

(72) Inventor : **Goto, Giichi**
6-11, Kofudai 5-chome, Toyono-cho
Toyono-gun, Osaka, 563-01 (JP)
Inventor : **Ohkawa, Shigenori**
45-20, Makamicho 6-chome
Takatsuki, Osaka, 569 (JP)
Inventor : **Fukumoto, Shoji**
21-72, Takenodai 1-chome, Nishi-ku
Kobe, Hyogo, 673 (JP)

(74) Representative : **Laredo, Jack Joseph et al**
Elkington and Fife Prospect House 8
Pembroke Road
Sevenoaks, Kent TN13 1XR (GB)

Jouve, 18, rue Saint-Denis, 75001 PARIS

Description

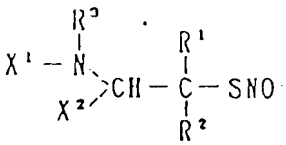
This invention relates to novel S-nitrosothiol derivatives which are useful as medicines, especially as therapeutics for the cardiovascular diseases such as hypertension and angina pectoris.

Along with aging of society, hypertension and heart diseases have become matters of primary concern, and various cardiovascular medicines have been developed for the treatment of such diseases. There are prior art documents disclosing the production of some nitro-compounds and nitrites among the medicines [Journal of Pharmacy and Pharmacology, 31, 801 (1979)].

In the social circumstances described above, more reasonable agents are being required to be developed in the field of cardiovascular drugs, particularly antihypertensives and therapeutics for angina pectoris. However, satisfactory compounds have not yet been found. There have been no report so far for the application of S-nitrosothiol derivatives as therapeutics for angina pectoris.

DETAILED DESCRIPTION

As a result of the research to find out useful compounds as therapeutics for cardiovascular diseases, especially as anti-hypertensives and therapeutics for angina pectoris, the present inventors have found that the compounds represented by the formula (1):



(I)

wherein R^1 and R^2 represent respectively a hydrogen atom or a hydrocarbon residue which may be substituted; R^3 is a hydrogen atom, an acyl group or a hydrocarbon residue which may be substituted; X^1 is a hydrogen atom, an acyl group, a lower alkoxy group or a hydrocarbon residue which may be substituted; X^2 is an acyl group or a carboxyl group which may be esterified or form an amide; and when X^2 is a carboxyl group X^1 is not a hydrogen atom or acetyl group, and when both R^1 and R^2 are hydrogen atoms X^1 is not acetyl group or gamma-glutamyl group, and the salts thereof are excellent in alleviation of the cardiovascular diseases, and have completed the present invention.

The "hydrocarbon residues" in the above-mentioned "hydrocarbon residues which may be substituted" in the formula (I) include, chain-, cyclic-, saturated-, and unsaturated-hydrocarbon residues, and various combinations thereof. Chain-hydrocarbon residues include straight chain and branched alkyl groups each having 1 to 6 carbon atoms (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, tert-butyl, n-pentyl, n-hexyl).

Chain unsaturated hydrocarbon residues include straight chain and branched C_{2-4}-alkenyl (e.g. vinyl, allyl, 2-butenyl), and C_{2-4}-alkynyl (e.g. propargyl, 2-butynyl).

Cyclic saturated hydrocarbon residues include monocyclic cycloalkyl having 3 to 7 carbon atoms (e.g. cyclobutyl, cyclopentyl, cyclohexyl), and bridged cyclic saturated hydrocarbon residues having 8 to 14 carbon atoms (e.g. bicyclo[3,2,1]oct-2-yl, bicyclo[3,3,1]nonan-2-yl). Cyclic unsaturated hydrocarbon residues include phenyl and naphthyl groups.

R^1 and R^2 may be bound with each other to form a ring of $-(CH_2)_n-$ wherein n is an integer of 2 to 6.

Substituents for these hydrocarbon residues include halogen atoms (e.g. chlorine, bromine, and iodine atoms), nitro, nitrile, hydroxyl, carboxyl, C_{1-4}-alkoxy (e.g. methyloxy, ethyloxy, propyloxy, butyloxy, isopropyloxy), C_{1-4}-alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio), amino, mono- or di-C_{1-4}-alkyl substituted amino (e.g. methylamino, ethylamino, propylamino, dimethylamino, diethylamino), mono- or di-aralkyl substituted amino (e.g. benzylamino, 2-hydroxyphenylmethylamino), mono-or di-pyridylcarbonyl substituted amino (e.g. 3-pyridylcarbonylamino), C_{1-4} alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isobutoxycarbonyl), hydroxycarbonyl, C_{1-6}-alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, butylcarbonyl), cycloC_{3-6}-alkylcarbonyl (e.g. cyclopentylcarbonyl, cyclohexylcarbonyl), carbamoyl, mono- or di-C_{1-4}-alkyl-substituted carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, diethylcarbamoyl, dibutylcarbamoyl), and phenyl, phenoxy, benzoyl, phenoxycarbonyl, phenylC_{1-4}-alkylcarbamoyl (e.g. benzylcarbamoyl, phenethylcarbamoyl) and phenylcarbamoyl which may have 1 to 4 substituents [substituents in the respective phenyl group include C_{1-4}-alkyl group (e.g. methyl, ethyl, propyl, butyl, isopropyl), halogen atom (e.g. chlorine, bromine, iodine atoms), hydroxyl, benzyloxy, amino, mono- or di-C_{1-4}-al-

kyl-substituted amino (e.g. methylamino, ethylamino, propylamino, dimethylamino, diethylamino, methylethylamino), nitro, C_{1-4}-alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl)].

The appropriate number of the substitutents in each of these hydrocarbon residues is 1 to 3.

Acyl groups represented by R^3, X^1, and X^2 include carboxylic acyl, carbamic acyl, sulfonic acyl, and substituted oxycarboxylic acyl groups, all of which may be substituted. When an acyl group is substituted, the substituents include those for the hydrocarbon residues described above.

Carboxylic acyl groups include C_{1-6}alkylcarbonyl such as formyl, acetyl, propionyl, butyryl, valeryl, hexanoyl, isobutyryl, and isovaleryl (which may be substituted, for example, with amino, 3-carbamoyl-1,4-dihydropyridin-1-yl, 3-carbamoyl-1-pyridyl, or phenoxy; substituted C_{1-6}-alkylcarbonyl groups are exemplified by phenoxyacetyl, 4-aminobutyryl, aminomethylcarbonyl, 2-(3-carbamoyl-1,4-dihydropyridin-1-yl)ethylcarbamoyl, and 2-(3-carbamoylpyridin-1-yl)ethylcarbamoyl), C_{3-8}cycloalkylcarbonyl such as cyclopentylcarbonyl and cyclohexylcarbonyl, C_{3-8}cycloalkyl-C_{1-6}alkylcarbonyl such as cyclopentylacetyl, C_{2-6}alkenyl or alkynylcarbonyl such as acryloyl, crotonoyl, 2-pentenoyl, 4-pentynoyl, 2-hexenoyl, 3-hexenoyl, and 2,4-hexadienoyl, arylcarbonyl such as benzoyl, and naphthoyl, pyridylcarbonyl such as nicotinoyl, and dihydropyridylcarbonyl [which may be substituted, for example, with C_{1-4}alkyl (e.g. methyl, ethyl, propyl, butyl), benzyl, methoxycarbonyl, 3-nitrophenyl, nitro, or 2-trifluorophenyl; substituted dihydropyridylcarbonyl groups are exemplified by N-C_{1-4}alkyl-1,4-dihydropyridine-3-carbonyl (e.g. N-methyl-1,4-dihydropyridine-3-carbonyl, N-ethyl-1,4-dihydropyridine-3-carbonyl, N-butyl-1,4-dihydropyridine-3-carbonyl), N-benzyl-1,4-dihydropyridine-3-carbonyl, 2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-ylcarbonyl, and 2,6-dimethyl-5-nitro-4-(2-trifluorophenyl-1,4-dihydropyridine-3-ylcarbonyl], pyridiniumcarbonyl (in which the nitrogen in the pyridine ring is substituted, for example with C_{1-4}alkyl (e.g. methyl, ethyl), or benzyl, and exemplified by C_{1-4}alkylpyridinium-3-carbonyl (e.g. methylpyridinium-3-carbonyl, ethylpyridinium-3-carbonyl, propylpyridinium-3-carbonyl), and benzylpyridinium-3-carbonyl).

Carbamic acyl groups include carbamoyl, mono- or di- substituted carbamoyl groups. The mono- and di-substituted carbamoyl groups include mono- and di-C_{1-4}alkylcarbamoyl such as methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, and dipropylcarbamoyl, mono- and di-C_{3-6}-alkenyl- and alkynylcarbamoyl such as allylcarbamoyl, 3-butenylcarbamoyl, 4-pentenylcarbamoyl, and diallylcarbamoyl, mono- and di-aromatic group carbamoyl such as phenylcarbamoyl, naphthylcarbamoyl, and diphenylcarbamoyl.

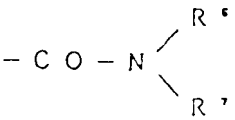
Sulfonic acyl groups include inorganic sulfonyl such as sodiumsulfonyl, C_{1-6}alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, propylsulfonyl, and butylsulfonyl, C_{2-6}alkenyl- or alkynylsulfonyl such as allylsulfonyl, and 2-methyl-2-propenesulfonyl, and aromatic sulfonyl such as phenylsulfonyl, p-methylphenylsulfonyl, and naphthalenesulfonyl.

Substituted oxycarboxylic acyl groups include C_{1-6}alkyloxycarbonyl which may be substituted with halogen (e.g. chlorine, bromine, iodine), cyano, benzyloxy, phenoxy, diC_{1-3}alkylamino (e.g. dimethylamino, diethylamino, dipropylamino), C_{1-4}alkyloxy (e.g. methyloxy, ethyloxy, butyloxy, t-butyloxy), C_{1-3}alkylthio (e.g. methylthio, ethylthio, propylthio), 4-(3-nitrophenyl)-2,6-dimethyl-3-methoxycarbonyl-1,4-dihydropyridin-5-ylcarbonylamino or dihydropyridylcarbonylamino (methyloxycarbonyl, ethyloxycarbonyl, n-propyloxycarbonyl, i-propyloxycarbonyl, n-butyloxycarbonyl, sec-butyloxycarbonyl, t-butyloxycarbonyl, n-hexyloxycarbonyl, 2-fluoroethyloxycarbonyl, 2-chloroethyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl, and 3-methyl-1,4-dihydropyridin-1-ylcarbonylaminomethyloxycarbonyl), C_{3-8}cycloalkyloxycarbonyl (which may be substituted, for example, with halogen such as chlorine, bromine, and iodine) such as cyclopentyloxycarbonyl, and cyclohexyloxycarbonyl, C_{3-8}cycloalkyl-C_{1-6}alkyloxycarbonyl such as cyclopentylmethyloxycarbonyl, C_{2-7}alkenyl- or alkynyloxycarbonyl such as allyloxycarbonyl, crotyloxycarbonyl, and 2-pentene-1-oxycarbonyl, aromatic or aromatic-aliphatic oxycarbonyl (which may be substituted, for example, with halogen such as chlorine, bromine and iodine, or nitro) such as phenyloxycarbonyl, benzyloxycarbonyl, and phenethyloxycarbonyl, and quinuclidinyl.

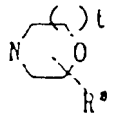
Lower alkoxy groups represented by X^1 include those represented by the formula: -OR^4 [wherein R^4 represents an alkyl group having 1 to 6 carbon atoms (e.g. methyl, ethyl, propyl, i-propyl, butyl, tert-butyl, hexyl)].

Esterified carboxyl groups represented by X^2 include those represented by the formula: -CO-OR^5 [wherein R^5 represents a hydrocarbon residue which may be substituted], and the "hydrocarbon residues which may be substituted" represented by R^5 include the groups described above as "the hydrocarbon residues which may be substituted" represented by R^1, R^2, R^3, or X^1.

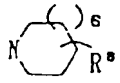
Amide-forming carboxyl groups represented by X^2 include those represented by the formula:



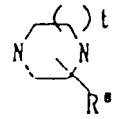
wherein R^6 is a hydrogen atom or a hydrocarbon residue which may be substituted, and R^7 is a hydrogen atom or a lower alkyl group. In the formula described above, the "hydrocarbon residues which may be substituted" represented by R^6 include the "hydrocarbon residues which may be substituted" represented by R^1, R^2, R^3, R^5, or X^1, described above, and the lower alkyl groups represented by R^7 include alkyl groups having 1 to 6 carbon atoms each (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, tert-butyl, n-pentyl, n-hexyl). In the formula described above, R^6 and R^7 may constitute a cyclic amino group together with the adjacent nitrogen atom, and the cyclic amino groups formed by R^6, R^7, and the adjacent nitrogen atom include nitrogen-containing 5- to 7-membered heterocyclic groups, such as the groups represented by the formula:



those represented by the formula:

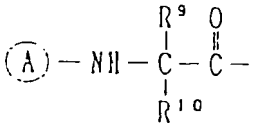


and those represented by the formula:

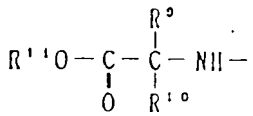


In these formula, s represents 0, 1, or 2, t represents 1, or 2, and R^8 represents a substituent which the cyclic amino group formed by the R^6, and R^7 may have, or a hydrogen atom; the substituents include alkyl groups having 1 to 3 carbon atoms each (e.g. methyl, ethyl, propyl), oxo, hydroxy, phenyl, benzyl, and amino groups.

The groups represented by the formula:



as X^1 when X^1 represents an acyl group, and the groups represented by the formula:



as the substituted amino groups when X^2 represents an amide-forming carboxyl group, represent the residues of amino acid derivatives, where the amino acids are not specified. The amino acids may be of D-form or L-form. R^9, R^{10}, and R^{11} are the same or different, each representing a hydrogen atom or a lower alkyl group

which may be substituted. R^9 and R^{10} may bind to each other to form a lower alkylene chain represented by the formula: $-(CH_2)_m-$ (wherein m represents an integer of 2 to 4), and Ⓐ represents a hydrogen atom, lower alkyl group, or acyl group.

The residues of amino acid derivatives described above include those of derivatives of amino acids such as glycine, alanine, glutamic acid, leucine, isoleucine, phenylalanine, aspartic acid, cysteine, sarcosine, glutamine, asparagine, and proline.

When the compound of the general formula (I) has an asymmetric carbon atom, the compound may be of D-, L- or DL-form, being unaffected by the asymmetry of the group represented by X^1 or X^2.

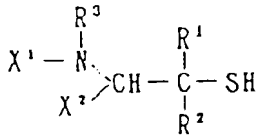
Among the compounds represented by the formula (I) described above, those excellent in chemical stability are desirable, and R^1 and R^2 may be any group that has a steric effect contributing to stabilization of -SNO group, being desirably a C_{1-6}alkyl group such as methyl, ethyl, or propyl, phenyl, or naphthyl; when R^1 and R^2 are bound to each other, the group formed by R^1 and R^2 together with the carbon atoms to which the groups are bound is desirably cyclopentyl or cyclohexyl.

R^3 is desirably a hydrogen atom, or a C_{6-10}aromatic acyl group such as benzoyl, naphthoyl, or phenylacetyl. X^1 is desirably a hydrogen atom or an amino acid residue, and the amino acid is desirably glycine, aspartic acid, phenylalanine, asparagine, glutamic acid, or glutamine. X^2 is desirably carboxyl, carbonylamino, or carboxyl forming an amide with an amino acid residue, and the amino acid is desirably glycine, asparagine, glutamine, aspartic acid, glutamic acid, or phenylalanine.

Among the compounds represented by the formula (I) described above, are desirable those wherein each of R^1 and R^2 represents C_{1-6}alkyl group, phenyl, or naphthyl, or R^1 and R^2 form cyclopentyl or cyclohexyl together with the carbon atoms to which R^1 and R^2 are bound, R^3 is a hydrogen atom or a C_{6-10} aromatic acyl group, X^1 is a hydrogen atom or an amino acid residue of which amino acid is selected from the group consisting of glycine, aspartic acid, phenylalanine, asparagine, glutamic acid, and glutamine, X^2 is a carboxyl group, carbonylamino or a carboxyl group forming an amide with an amino acid residue of which amino acid is selected from the group consisting of glycine, aspartic acid, asparagine, glutamic acid, glutamine, and phenylalanine.

When the compound (I) of this invention is basic, the compound may form an acid adduct, especially a physiologically acceptable acid adduct; such adducts are exemplified by salts with inorganic acids (e.g. hydrochloric acid, nitric acid, phosphoric acid, hydrobromic acid), and salts with organic acids (e.g. acetic acid, propionic acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid).

The compounds of the general formula (I) can be produced by nitrosation of the compounds represented by the general formula (II).



(II)

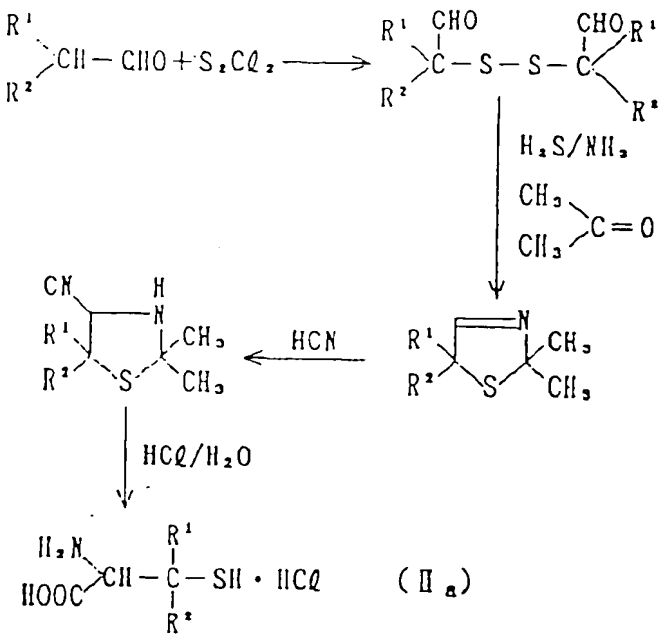
wherein R^1, R^2, R^3, X^1, and X^2 mean the same as described above.

Reagents generally used for the nitrosation of the compound (II) include nitrogen monoxide, nitrogen dioxide, dinitrogen tetraoxide, nitrosyl chloride, nitrous acid, and ethyl nitrite, but the reagents are not limited to these, and any reagent that can usually be used for nitrosation may be used.

The reaction may be conducted without any solvent or in a solvent. Any solvent may be used as far as it does not inhibit nitrosation, including water, alcohols (e.g. methanol, ethanol, propanol, butanol, tert-butanol), petroleum-composing solvents (e.g. n-hexane, n-pentane, n-heptane), aromatic solvents (e.g. benzene, toluene, pyridine), ethers (e.g. ethyl ether, tetrahydrofuran, dioxane, isopropyl ether), amides (e.g. N,N-dimethylformamide, N,N-dimethylacetamide), esters (e.g. methyl acetate, ethyl acetate, butyl acetate), halogenated hydrocarbons (e.g. dichloromethane, chloroform, dichloroethane, carbon tetrachloride), and dimethyl sulfoxide.

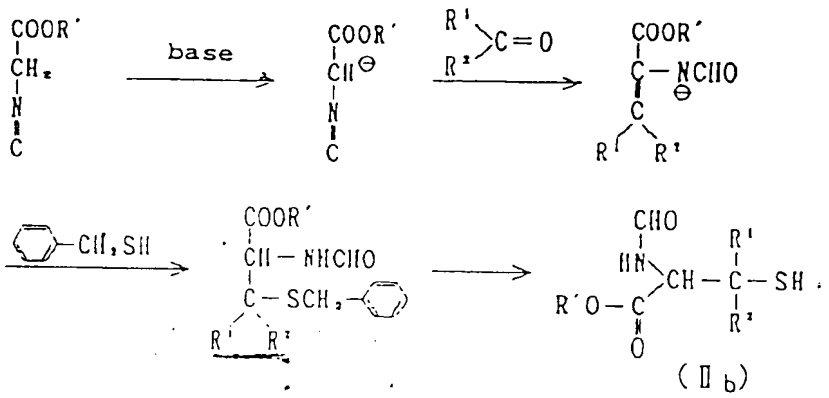
The reaction can be conducted at -30°C to 150°C, but is desirably conducted at a lower temperature (-5°C to 30°C). For one mole of the compound (II), desirably 1 to 5 moles of the nitrosating reagent are used. The reaction time varies depending on the properties of the compound (II) being generally 1 minute to 6 hours, desirably as short as 1 minute to 30 minutes.

The compounds (II) can be produced according to the per se known method [Angewandte Chemie, 87, 372 (1975)], for example, by the procedures shown as the Reaction Formulas 1 to 4.



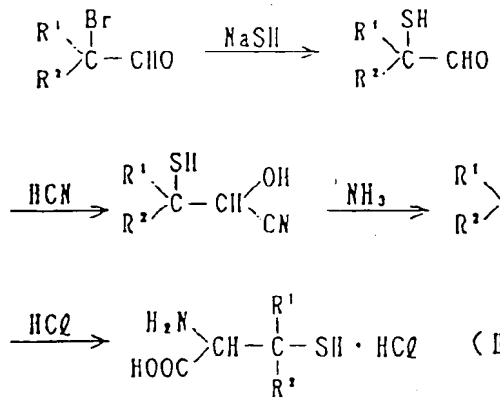
wherein the symbols are the same as described above.

Reaction Formula 1



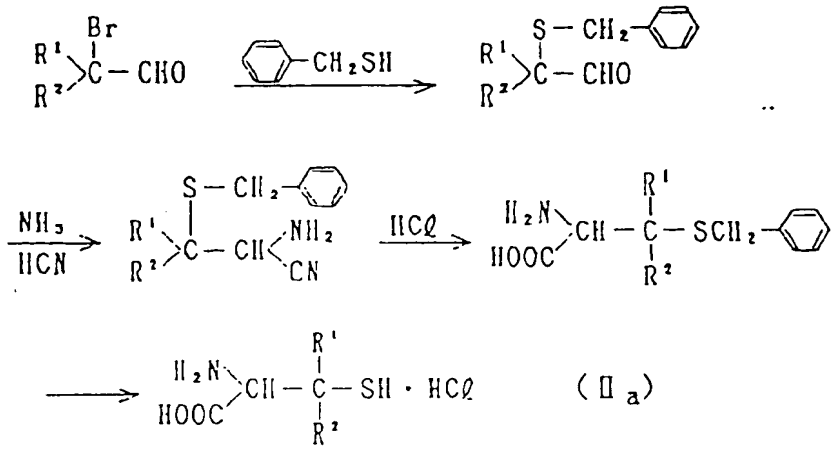
wherein R' is a C_{1-6}lower alkyl or benzy, and other symbols are the same as described above.

Reaction Formula 2



wherein the symbols are the same as described above.

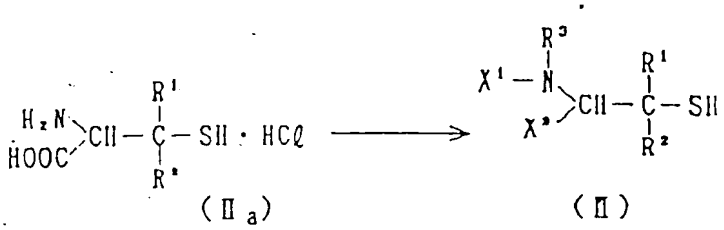
Reaction Formula 3



wherein the symbols are the same as described above.

Reaction Formula 4

The compound (IIa) or (IIb) thus obtained is further subjected to N-acylation, N-alkylation, N-peptide formation, or esterification, alkylation, or peptide formation at the C terminal, to give the compound (II).



These reactions can be conducted according to the per se known method.

The compounds (I) of this invention act on the cardiovascular system of mammals, exerting excellent hypotensive action, anti-arrhythmic action, anti-anginal action, cardiotonic action, or coronary vasodilation.

The compounds (I) of this invention are excellent in duration and strength of the cardiovascular action as

compared with the known nitro compounds such as nitroglycerine and nitrites, having no or only very mild undesirable side effects in the cardiovascular, psychic-nervous, or digestive system, such as dizziness, palpation, discomfort in the chest, arrhythmia, headache, fatigue, nausea, and vomiting. The compounds are remarkably effective after oral, parenteral, or percutaneous administration. Therefore the compounds are useful as therapeutics or prophylactics for various cardiovascular disorders in mammals including humans. Among the compounds (I) of this invention, those that dilate selectively the coronary vessels are useful as the prophylactics and therapeutics for angina pectoris.

The diseases for which the compounds (I) of this invention are useful include angina pectoris, myocardial infarction, cardiac asthma, achalasia (temporary remission), coronary sclerosis (chronic ischemic heart disease, asymptomatic ischemic heart disease, arteriosclerotic heart disease), maintaining hypotensive state during operation, emergency treatment of abnormal hypertension during operartion, acute heart failure, essential hypertension, and renal hypertension; the compounds can be used for prevention and treatment of these diseases.

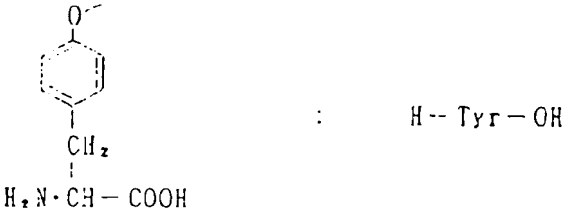
The compounds of this invention as such or a stabilized conjugate thereof with cyclodextrin, etc. can be administered to mammals including human orally or parenterally in various forms such as tablets, granules, capsules, injections, suppositories, percutaneous preparations, buccal preparations (sublingual tablets), ointments, and cataplasms. The dose varies depending on the type of the disease to be treated and the symptom, the daily dose being generally 0.1 mg to 500 mg, desirably 1 mg to 30 mg for oral administration to an adult human.

In this specification, amino acids, protective groups, and others are sometimes shown by conventionally used abbreviations based on the IUPAC-IUB Commission on Biological Nomenclature. The abbreviations used are listed in the following.

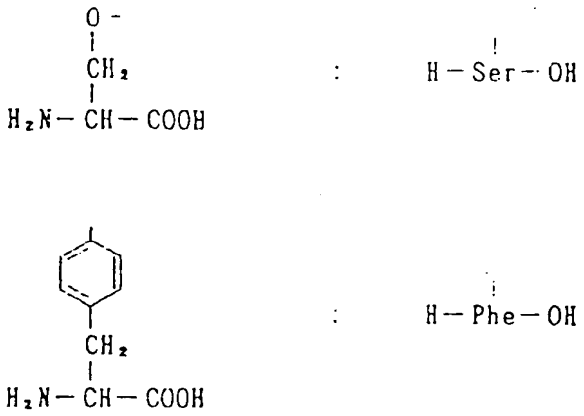
Ac:	acetyl
Boc:	t-butoxycarbonyl
OBzl:	benzylester
WSC:	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
HOBt:	1-hydroxy-benzotriazole
Trt:	trityl
Pen:	penicillamine
Gly:	glycine
Ala:	alanine
Val:	valine
Leu:	leucine
Pro:	proline
Phe:	phenylalanine
Tyr:	tyrosine
Glu:	glutamic acid
Asp:	aspartic acid

The side chains of amino acid residues are represented as follows:

: H — Pen — OH



: H -- Tyr — OH



EXAMPLES

The following Reference Examples, Working Examples, Preparation Examples, and Experimental Examples explain this invention in more detail, but should not limit this invention.

Reference Example 1 (Synthesis of the Compound A-1)

To the solution of S-trityl-L-penicillamine (69.5 g) and di-t-butyldicarbonate (46.5 g) in dichloromethane (1500 ml), was added triethylamine (20.2 ml) at 0°C, and the mixture was stirred at room temperature for 5 hours. To the reaction mixture were added ice and an aqueous solution of potassium hydrogensulfate. The organic layer was washed with an aqueous solution of potassium hydrogensulfate, water, and saturated saline, in this order, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, to give N-t-butoxycarbonyl-S-trityl-L-penicillamine (87.0 g).

In the same way the Compound A-2 listed in Table 1 described below was synthesized.

Reference Example 2 (Synthesis of the Compound B-1)

To the solution of N-t-butoxycarbonyl-S-trityl-D-penicillamine (A-2) (6.0 g) in dimethylformamide (40 ml), were added methyl iodide (1.5 ml) and potassium hydrogencarbonate (2.4 g), and the mixture was stirred for 14 hours. To the reaction mixture was added ice-water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and then with saturated saline, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, to give N-t-butoxycarbonyl-S-trityl-D-penicillamine methyl ester (6.0 g).

Reference Example 3 (Synthesis of the Compound B-2)

To the solution of N-t-butoxycarbonyl-S-trityl-L-penicillamine (A-1) (4.0 g) and 1-hydroxy-benzotriazole (abbreviated as HOBt) (1.2 g) in chloroform (40 ml) and tetrahydrofuran (16 ml), was added dropwise by ice-cooling the solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (water-soluble carbodiimide: abbreviated as WSC) (1.7 g) in chloroform (10 ml). The mixture was stirred at the same temperature for 1 hour, to which glycine ethyl ester hydrochloride (1.1 g) and triethylamine (0.85 ml) were added, and the mixture was stirred at room temperature for 12 hours. After addition of water, the organic layer was washed with an aqueous solution of potassium hydrogensulfate, water, an aqueous solution of sodium hydrogencarbonate, water and saturated saline, in this order, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, and the residue was subjected to column chromatography, to give N-t-butoxycarbonyl-S-trityl-L-penicillamylglycine ethyl ester (4.5 g).

In the same way the Compounds B-3 to B-22 and D-30 listed in Table 1 described below were synthesized.

Reference Example 4 (Synthesis of the Compound C-2)

To the solution of N-t-butoxycarbonyl-S-trityl-L-penicillamylglycine ethyl ester (B-2) (4.5 g) and 2,6-lutidine (2.8 ml) in dichloromethane (100 ml), was added dropwise at 0°C the solution of trimethylsilyl trifluorometha-

nesulfonate (3.9 ml), and the mixture was stirred for 1 hour while the temperature was gradually returned to room temperature. To the reaction mixture was added ice-water, and the organic layer was washed with 1N-hydrochloric acid, water, an aqueous solution of sodium hydrogencarbonate, water, and saturated saline, in this order, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, to give S-trityl-L-penicillamylglycine ethyl ester (3.8 g)

In the same way the Compounds C-1, and C-3 to C-22 listed in Table 1 described below were synthesized.

Reference Example 5 (Synthesis of the Compound D-3)

To the solution of S-trityl-L-penicillamylglycine ethyl ester (C-2) (3.7 g) in dichloromethane (50 ml) were added acetyl chloride (0.66 ml) and triethylamine (0.88 ml) at 0°C. The mixture was stirred at the same temperature for 15 minutes and then ice water was added. The organic layer was washed with an aqueous potassium hydrogensulfate solution, water, an aqueous sodium hydrogencarbonate solution, water and saturated saline, in this order, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, and the residue was subjected to silica gel column chromatography, to give N-acetyl-S-trityl-L-penicillamylglycine ethyl ester (3.5 g).

Reference Example 6 (Synthesis of the Compound D-4)

To the solution of S-trityl-L-penicillamylglycine ethyl ester (C-2) (5.4 g) and N-t-butoxycarbonyl-L-glutamic acid-α-benzyl ester (3.8 g) in chloroform (100 ml) was added WSC (2.4 g) at 0°C, and the mixture was stirred at room temperature for 3 hours. To the reaction mixture was added ice water. The organic layer was washed with an aqueous potassium hydrogensulfate solution, water, aqueous sodium hydrogencarbonate solution, water and saturated saline, in this order, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, and the residue was subjected to column chromatography, to give (4S)-4-t-butoxycarbonylamino-4-benzyloxycarbonylbutyryl-S-trityl-L-penicillamylglycine ethyl ester (8.4 g).

In the same way the Compounds D-1, D-2, D-5 to D-27 and D-29 listed in Table 1 described below were synthesized.

Reference Example 7 (Synthesis of the Compound E-5)

To the solution of (4S)-4-t-butoxycarbonylamino-4-benzyloxycarbonylbutyryl-S-trityl-L-penicillamylglycine ethyl ester (D-4) (8.4 g) in tetrahydrofuran (150 ml) was added 1N-sodium hydroxide (25.3 ml) and the mixture was stirred at room temperature for 2 hours. Tetrahydrofuran was evaporated off under reduced pressure, and the aqueous layer was washed twice with diethyl ether, to which an aqueous potassium hydrogensulfate solution was added to make it acidic, and the solution was extracted with ethyl acetate. The organic layer was washed with water and saturated saline, and the solvent was evaporated off under reduced pressure, to give [N-γ-(N-t-butoxycarbonyl)-L-glutamyl-S-trityl-L-penicillamyl]glycine (7.0 g).

In the same way the Compounds E-1 to E-4, and E-6 to E-32 listed in Table 1 described below were synthesized.

Reference Example 8 (Synthesis of the Compound F-5)

The solution of [N-γ-(N-t-butoxycarbonyl)-L-glutamyl-S-trityl-L-penicillamyl]glycine (E-5) (3.0 g) in chloroform (60 ml) was bubbled with hydrogen chloride gas at 0°C for 30 minutes. To the reaction mixture was added diethyl ether, and the crystals were collected by filtration and washed with diethyl ether. The crystals were dried under reduced pressure, to give (N-γ-L-glutamyl-L-penicillamyl)glycine hydrochloride (1.7 g).

In the same way the Compounds F-1 to F-4, and F-6 to F-32 listed in Table 1 described below were synthesized.

Reference Example 9 (Synthesis of the Compound B-23)

To the solution of N-t-butoxycarbonyl-S-trityl-L-penicillamine (A-1)(4.0g) and HOBt (1.2g) in chloroform (40mℓ) and tetrahydrofuran (15mℓ), was added dropwise under ice-cooling the solution of WSC (1.7g) in chloroform (10mℓ). The mixture was stirred at the same temperature for 1 hour, to which water was added, and the organic layer was washed with an aqueous solution of potassium hydrogensulfate, water, an aqueous solution of sodium hydrogencarbonate, water and saturated saline, in this order, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, to give HOBt ester.

To the solution of p-sulfophenylalanine (2.0g) in water (40mℓ), sodium hydrogencarbonate (2.1g) was added. To this solution, the solution of the HOBt ester synthesized as described above in dioxane (40mℓ) was added, followed by addition of tetrabutylammonium hydrogensulfate (3.3g), and the mixture was stirred at room temperature for 1 hour. The solvent was evaporated off under reduced pressure and the residue was extracted with chloroform. The organic layer was washed with an aqueous solution of potassium hydrogensulfate, water and saturated saline, in this order, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, to give tetrabutylammonium N-t-butoxycarbonyl-S-trityl-L-penicillamyl-P-sulfophenylalanine (7.5g).

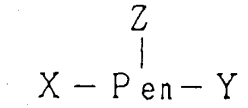
In the same way the Compound D-28 listed in Table 1 described below was synthesized.

Reference Example 10 (Synthesis of the Compound C-23)

To the solution of tetrabutylammonium N-t-butoxycarbonyl-S-trityl-L-penicillamyl-p-sulfophenylalanine (B-23)(7.5g) and 2,6-lutidine (3.8mℓ) in dichloromethane (100mℓ), was added dropwise at 0°C the solution of trimethylsylyl trifluoromethanesulfonate (5.5mℓ), and the mixture was stirred for 1 hour while the temperature was gradually returned to room temperature. The solvent was evaporated off under reduced pressure and the residue was washed with diethyl ether and acetone, in this order, to give S-trityl-L-penicillamyl-p-sulfophenylalanine (3.1g).

Table 1 shows the structure, physical properties, and NMR data of the Compounds A-1 to F-32 synthesized in the Reference Examples.

Table 1



Compound	X	Configuration of Pen	Y	Z	Molecular formula Physical properties	Related Ref. Ex.	NMR spectra TMS internal standard (δ, ppm) in $CDCl_3$
A-1	Boc	L	OH	Trt	$C_{29}H_{33}NO_4S$ amorphous	1	1.07(3H), 1.13(3H), 1.44(9H), 3.41(1H), 5.32(1H), 7.14-7.34 (9H), 7.50-7.70(6H), 8.20(1H)
A-2	Boc	D	OH	Trt	$C_{29}H_{33}NO_4S$ amorphous	1	1.06(3H), 1.12(3H), 1.44(9H), 3.46(1H), 4.90(1H), 5.37(1H), 7.10-7.36(9H), 7.56-7.70 (6H)
B-1	Boc	D	OMe	Trt	$C_{30}H_{35}NO_4S$ amorphous	2	1.02(2H), 1.07(3H), 1.45(9H), 3.54(1H), 3.36(3H), 5.37(1H), 7.10-7.33(9H), 7.53-7.70 (6H)

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Table 1 (continued)

B-2	Boc	L	Gly-OEt	Trt	$C_{33}H_{40}N_2O_5S$ amorphous	3	1.11(3H), 1.18(3H), 1.25(3H), 1.42(9H), 3.22(1H), 3.96(2H), 4.17(2H), 5.34(1H), 6.20(1H), 7.14-7.34(9H), 7.57-7.70(6H)
B-3	Boc	D	Gly-OEt	Trt	$C_{33}H_{40}N_2O_5S$ amorphous	3	1.10(3H), 1.13(3H), 1.22(3H), 1.42(9H), 3.43(1H), 3.95(2H), 4.14(2H), 5.47(1H), 6.53(1H), 7.11-7.34(9H), 7.57-7.70(6H)
B-4	Boc	L	L-Ala-OEt	Trt	$C_{34}H_{42}N_2O_5S$ amorphous	3	1.06(3H), 1.13(3H), 1.24(3H), 1.38(3H), 1.43(9H), 3.38(1H), 4.15(1H), 4.49(1H), 5.36(1H), 6.38(1H), 7.14-7.40(9H), 7.56-7.70(6H)
B-5	Boc	L	L-Val-OMe	Trt	$C_{35}H_{44}N_2O_5S$ amorphous	3	0.88(3H), 0.92(3H), 1.05(3H), 1.16(3H), 1.42(9H), 2.13(1H), 3.31(1H), 3.66(3H), 4.47(1H), 5.33(1H), 6.34(1H), 7.15-7.38 (9H), 7.55-7.73(6H)

Table 1 (continued)

B-6	Boc	D	L-Val-OMe	Trt	$C_{35}H_{44}N_2O_5S$ amorphous	3	0.87(3H), 0.90(3H), 1.05(3H), 1.17(3H), 1.43(9H), 2.12(1H), 3.29(1H), 3.70(3H), 4.48(1H), 5.34(1H), 6.37(1H), 7.16-7.38 (9H), 7.58-7.68(6H)
B-7	Boc	L	L-Leu-OEt	Trt	$C_{37}H_{48}N_2O_5S$ amorphous	3	0.91(6H), 1.02(3H), 1.14(3H), 1.22(3H), 1.42(9H), 1.30-1.80 (3H), 3.45(1H), 4.13(2H), 4.55 (1H), 5.33(1H), 6.23(1H), 7.10-7.40(9H), 7.50-7.75(6H)
B-8	Boc	L	L-Pro-OMe	Trt	$C_{35}H_{42}N_2O_5S$ amorphous	3	1.12(3H), 1.14(3H), 1.44(9H), 1.82-2.32(4H), 3.27-3.66(2H), 3.64(3H), 3.97(1H), 4.47(1H), 5.40(1H), 7.12-7.33(9H), 7.56-7.66(6H)
B-9	Boc	L	L-Phe-OEt	Trt	$C_{40}H_{46}N_2O_5S$ amorphous	3	1.03(3H), 1.09(3H), 1.16(3H), 1.43(9H), 3.07(2H), 3.20(1H), 4.09(2H), 4.81(1H), 5.29(1H), 6.29(1H), 7.04-7.38(14H), 7.52-7.73(6H)

Table 1 (continued)

B-10	Boc	L	L-Tyr-OEt	Trt	$C_{40}H_{46}N_2O_8S$ amorphous	3	1.02(3H), 1.07(3H), 1.18(3H), 1.44(9H), 2.98(2H), 3.26(1H), 4.09(2H), 4.75(1H), 5.39(1H), 5.87(1H), 6.63(2H), 6.94(2H), 7.12-7.32(10H), 7.55-7.64(6H)
B-11	Boc	L	L-Glu(OEt)-OEt	Trt	$C_{38}H_{48}N_2O_7S$ amorphous	3	1.04(3H), 1.17(3H), 1.24(6H), 1.43(9H), 1.80-2.50(4H), 3.23(1H), 4.09(2H), 4.15(2H), 4.54(1H), 5.32(1H), 6.38(1H), 7.13-7.34(9H), 7.57-7.67(6H)
B-12	Boc	L	$NHCHPh_2$	Trt	$C_{42}H_{44}N_2O_3S$ m.p. 158.0-159.0	3	0.98(3H), 1.15(3H), 1.41(9H), 3.60(1H), 5.29(1H), 6.15(1H), 6.41(1H), 7.12-7.34(9H), 7.48-7.58(6H)
B-13	Boc	L	L-Asp(OBzl)-OBzl	Trt	$C_{47}H_{50}N_2O_7S$ amorphous	3	1.05(3H), 1.12(3H), 1.41(9H), 2.85(1H), 2.94(2H), 4.80(1H), 5.02(2H), 5.07(2H), 5.25(1H), 6.11(1H), 7.12-7.40(19H), 7.56-7.67(6H)

Table 1 (continued)

B-14	Boc	L	L-Met-OEt	Trt	$C_{36}H_{46}N_2O_5S_2$ amorphous	3	1.06(3H), 1.17(3H), 1.24(3H), 1.43(9H), 1.25-2.24(2H), 2.05(3H), 2.50(2H), 3.22(1H), 4.16(2H), 4.61(1H), 5.31(1H), 6.40(1H), 7.15-7.40(9H), 7.57-7.67(6H)
B-15	Boc	L	L-Ile-OMe	Trt	$C_{36}H_{48}N_2O_5S$ amorphous	3	0.89(6H), 1.03(3H), 1.16(3H), 1.35-1.52(2H), 1.42(9H), 1.86(1H), 3.34(1H), 3.66(3H), 4.52(1H), 5.32(1H), 6.38(1H), 7.15-7.42(9H), 7.53-7.73(6H)
B-16	Boc	D	$NHCHPh_2$	Trt	$C_{42}H_{44}N_2O_3S$ m.p. 158.0-159.0	3	0.98(3H), 1.15(3H), 1.41(9H), 3.60(1H), 5.28(1H), 6.15(1H), 6.40(1H), 7.10-7.40(19H), 7.48-7.57(6H)
B-17	Boc	D	L-Leu-OEt	Trt	$C_{37}H_{48}N_2O_5S$ amorphous	3	0.82-0.91(6H), 1.05(3H), 1.15(3H), 1.24(3H), 1.42(9H), 1.30-1.81(3H), 3.34(1H), 4.14(2H), 4.51(1H), 5.33(1H), 6.13(1H), 7.15-7.33(9H), 7.56-7.63(6H)

Table 1 (continued)

B-18	Boc	D	L-Phe-OEt	Trt	$C_{40}H_{46}N_2O_5S$ amorphous	3	0.99(3H), 1.11(3H), 1.14(3H), 1.42(9H), 2.93-3.16(2H), 3.34(1H), 4.08(2H), 4.77(1H), 5.27(1H), 6.32(1H), 7.08-7.33(14H), 7.54-7.63(6H)
B-19	Boc	D	L-Glu(OEt)-OEt	Trt	$C_{38}H_{48}N_2O_7S$ amorphous	3	1.08(3H), 1.17(3H), 1.20(3H), 1.25(3H), 1.42(9H), 1.82-2.43(4H), 3.20(1H), 4.07(2H), 4.16(2H), 4.53(1H), 5.34(1H), 6.39(1H), 7.15-7.36(9H), 7.56-7.68(6H)
B-20	Boc	L	L-Ser-OMe	Trt	$C_{34}H_{40}N_2O_6S$ amorphous	3	1.12(3H), 1.34(3H), 1.41(9H), 2.06(1H), 3.68-4.10(2H), 3.76(3H), 4.38(1H), 5.21(1H), 6.06(1H), 7.19-7.38(10H), 7.63-7.73(6H)
B-21	Boc	D	L-Pro-OMe	Trt	$C_{35}H_{42}N_2O_5S$ amorphous	3	0.94(6H), 1.45(9H), 1.80-2.22(4H), 3.43-3.91(2H), 3.70(3H), 4.38-4.49(2H), 5.43(1H), 7.10-7.32(9H), 7.51-7.63(6H)

Table 1 (continued)

B-22	Boc	L	CH_2COOEt Tyr-OEt	Trt	$C_{44}H_{52}N_2O_8S$ amorphous	3	1.03(3H), 1.10(3H), 1.17(3H), 1.30(3H), 1.43(9H), 3.00(2H), 3.16(1H), 4.07(2H), 4.27(2H), 4.58(2H), 4.73(1H), 5.29(1H), 6.27(1H), 6.78(2H), 7.05(2H), 7.12-7.30(9H), 7.55-7.64(6H)
B-23	Boc	L	$SO_3 \cdot Bu_4N$ DL-Phe-OH	Trt	$C_{54}H_{77}N_3O_8S_2$ amorphous	9	0.92(12H), 1.05(3H), 1.07(3H) 1.23-1.66(16H), 1.43(9H), 3.02-3.26(1H), 4.62-4.75(1H), 5.36-5.45(1H), 6.37(1H), 7.10-7.43(12H), 7.56-7.78(8H)
C-1	H	D	OMe	Trt	$C_{25}H_{27}NO_2S$ oily	4	1.07(3H), 1.11(3H), 1.63(2H), 2.33(1H), 3.54(3H), 7.12-7.32 (9H), 7.56-7.68(6H)

Table 1 (continued)

C-2	H	L	Gly-OEt	Trt	$C_{28}H_{32}N_2O_3S$ amorphous	4	1.24(3H), 1.27(3H), 1.29(3H), 1.64(2H), 1.81(2H), 3.87(2H), 4.16(2H), 6.95(1H), 7.13-7.34 (9H), 7.63-7.73(6H)
C-3	H	D	Gly-OEt	Trt	$C_{28}H_{32}N_2O_3S$ amorphous	4	1.25(3H), 1.27(3H), 1.29(3H), 1.62(2H), 1.80(1H), 3.88(2H), 4.16(2H), 6.96(1H), 7.16-7.37 (9H), 7.62-7.73(6H)
C-4	H	L	L-Ala-OEt	Trt	$C_{29}H_{34}N_2O_3S$ amorphous	4	1.23(3H), 1.24(3H), 1.26(3H), 1.30(3H), 1.62(2H), 1.78(1H), 4.14(2H), 4.39(1H), 6.84(1H), 7.15-7.36(9H), 7.63-7.73(6H)
C-5	H	L	L-Val-OMe	Trt	$C_{30}H_{36}N_2O_3S$ amorphous	4	0.84(3H), 0.87(3H), 1.25(3H), 1.26(3H), 1.64(2H), 1.79(1H), 2.10(1H), 3.68(3H), 4.36(1H), 6.80(1H), 7.14-7.34(9H), 7.62-7.73(6H)

Table 1 (continued)

C-6	H	D	L-Val-OMe	Trt	$C_{30}H_{36}N_2O_3S$ amorphous	4	0.83(3H), 0.86(3H), 1.24(3H), 1.29(3H), 1.80(1H), 2.06(1H), 2.09(2H), 3.69(3H), 4.31(1H), 6.67(1H), 7.16-7.36(9H), 7.64-7.73(6H)
C-7	H	L	L-Leu-OEt	Trt	$C_{32}H_{40}N_2O_3S$ amorphous	4	0.80-1.00(6H), 1.23(6H), 1.24 (3H), 1.35-1.73(3H), 1.65(2H), 1.84(1H), 4.12(2H), 4.36-4.49 (1H), 6.73(1H), 7.14-7.35(9H), 7.61-7.73(6H)
C-8	H	L	L-Pro-OMe	Trt	$C_{30}H_{34}N_2O_3S$ amorphous	4	1.29(3H), 1.34(3H), 1.60-2.22 (4H), 1.84(2H), 2.61(1H), 2.96 (2H), 3.63(3H), 4.35(1H), 7.05-7.42(9H), 7.50-7.78(6H)
C-9	H	L	L-Phe-OEt	Trt	$C_{35}H_{38}N_2O_3S$ amorphous	4	1.08(3H), 1.18(3H), 1.19(3H), 1.58(2H), 1.62(1H), 3.00(2H), 4.11(2H), 4.69(1H), 6.67(1H), 7.01-7.38(4H), 7.59-7.70(6H)

Table 1 (continued)

C-10	H	L	L-Tyr(SiMe$_3$)-OEt	Trt	$C_{38}H_{48}N_2O_4SSi$ amorphous	4	0.26(9H), 1.09(3H), 1.18(6H), 1.60(2H), 1.63(1H), 2.93(2H), 4.10(2H), 4.64(1H), 6.67(1H), 6.75(2H), 6.95(2H), 7.10-7.38 (9H), 7.60-7.70(6H)
C-11	H	L	L-Glu(OEt)-OEt	Trt	$C_{33}H_{40}N_2O_5S$ amorphous	4	1.23(6H), 1.24(6H), 1.64(2H), 1.84(1H), 1.80-2.43(4H), 4.10 (2H), 4.14(2H), 4.42(1H), 6.98 (1H), 7.15-7.36(9H), 7.63-7.72 (6H)
C-12	H	L	NHCHPh$_2$	Trt	$C_{37}H_{36}N_2OS$ amorphous	4	1.20(3H), 1.21(3H), 1.62(2H), 1.97(1H), 6.07(1H), 7.10-7.32 (20H), 7.60-7.70(6H)
C-13	H	L	L-Asp(OBzl)-OBzl	Trt	$C_{42}H_{42}N_2O_5S$ amorphous	4	1.17(6H), 1.50(1H), 1.58(2H), 2.72(1H), 3.04(1H), 4.76(1H), 4.96-5.17(4H), 6.91(1H), 7.08-7.44(19H), 7.55-7.77(6H)

Table 1 (continued)

C-14	H	L	L-Met-OEt	Trt	$C_{31}H_{38}N_2O_3S_2$ amorphous	4	1.12-1.34(9H), 1.63(2H), 1.84(1H), 1.80-2.20(2H), 2.05(3H), 2.44(2H), 4.16(2H), 4.52(1H), 7.01(1H), 7.13-7.42(9H), 7.56-7.79(6H)
C-15	H	L	L-Ile-OMe	Trt	$C_{31}H_{38}N_2O_3S$ amorphous	4	0.73-0.94(6H), 0.96-1.93(3H), 1.04(3H), 1.17(3H), 1.61(2H), 1.79(1H), 3.68(3H), 4.41(1H), 6.82(1H), 7.14-7.38(9H), 7.56-7.74(6H)
C-16	H	D	$NHCHPh_2$	Trt	$C_{37}H_{36}N_2OS$ amorphous	4	1.21(3H), 1.22(3H), 1.59(2H), 1.96(1H), 6.06(1H), 7.06-7.35 (19H), 7.53(1H), 7.58-7.68(6H)
C-17	H	D	L-Leu-OEt	Trt	$C_{32}H_{40}N_2O_3S$ amorphous	4	0.88(6H), 1.23(3H), 1.25(3H), 1.28(3H), 1.40-1.74(3H), 1.61(2H), 1.88(1H), 4.13(2H), 4.38(1H), 6.81(1H), 7.15-7.37(9H), 7.57-7.72(6H)

Table 1 (continued)

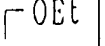
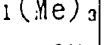
C-18	H	D	L-Phe-OEt	Trt	$C_{35}H_{38}N_2O_3S$ amorphous	4	1.17(3H), 1.20(3H), 1.23(3H), 1.48(2H), 1.71(1H), 3.00(2H), 4.10(2H), 4.65(1H), 6.88(1H), 7.00-7.36(14H), 7.67-7.72(6H)
C-19	H	D	 L-Glu-OEt	Trt	$C_{33}H_{40}N_2O_5S$ oily	4	1.23(3H); 1.24(6H), 1.27(3H), 1.60(2H), 1.82(1H), 1.80-2.42(4H), 4.08(2H), 4.14(2H), 4.39(1H), 6.97(1H), 7.14-7.36(9H) 7.62-7.73(6H)
C-20	H	L	 L-Ser-OMe	Trt	$C_{32}H_{40}N_2O_4SSi$ amorphous	4	0.08(9H), 1.27(3H), 1.29(3H), 1.62(2H), 1.67(1H), 3.61-3.98(2H), 3.68(3H), 4.50(1H), 6.79(1H), 7.15-7.37(9H), 7.65-7.74(6H)
C-21	H	D	L-Pro-OMe	Trt	$C_{30}H_{34}N_2O_3S$ amorphous	4	1.05(3H), 1.31(3H), 1.60-2.12(4H), 1.82(2H), 2.90(1H), 2.90-3.32(2H), 3.68(3H), 4.25-4.32(1H), 7.12-7.34(9H), 7.57-7.68(6H)

Table 1 (continued)

C-22	H	L	CH_2COOEt Tyr-OEt	Trt	$C_{39}H_{44}N_2O_6S$ amorphous	4	1.09(3H), 1.18(3H), 1.20(3H), 1.31(3H), 1.55(2H), 1.64(1H), 2.95(2H), 4.11(2H), 4.28(2H), 4.60(2H), 4.53-4.76(1H), 6.69(1H), 6.82(2H), 7.01(2H), 7.07-7.31(9H), 7.58-7.69(6H)
C-23	H	L	SO_3H DL-Phe-OH	Trt	$C_{33}H_{34}N_2O_6S_2$ amorphous	10	*0.99(3H), 1.11(3H), 2.09(2H), 2.10(1H), 3.01(2H), 4.39(1H), 7.16-8.52(22H)
D-1	Boc-L-Glu-OBzl	D	OMe	Trt	$C_{42}H_{48}N_2O_7S$ amorphous	6	1.01(3H), 1.12(3H), 1.41(9H), 1.70-2.45(4H), 3.65(3H), 3.85(1H), 4.35(1H), 5.16(2H), 5.34(1H), 6.54(1H), 7.13-7.37(14H), 7.54-7.62(6H)
D-2	Boc-D-Glu-OMe	D	OMe	Trt	$C_{36}H_{44}N_2O_7S$ amorphous	6	1.02(3H), 1.13(3H), 1.44(9H), 1.70-2.45(4H), 3.68(3H), 3.72(3H), 3.81(1H), 4.33(1H), 5.29(1H), 6.38(1H), 7.14-7.32(9H), 7.53-7.68(6H)

Table 1 (continued)

D-3	Ac	L	Gly-OEt	Trt	$C_{30}H_{34}N_2O_4S$ amorphous	5	1.11(3H), 1.15(3H), 1.25(3H), 1.98(3H), 3.77(1H), 3.95(2H), 4.18(2H), 6.23-6.36(2H), 7.16-7.35(9H), 7.58-7.67(6H)
D-4	Boc-L-Glu-OBzl	L	Gly-OEt	Trt	$C_{45}H_{53}N_3O_8S$ amorphous	6	1.12(3H), 1.19(3H), 1.25(3H), 1.41(9H), 1.55-2.26(4H), 3.57(1H), 3.94(2H), 4.17(2H), 4.33(1H), 5.12(2H), 5.38(1H), 6.23(1H), 6.36(1H), 7.14-7.44(14H), 7.54-7.76(6H)
D-5	Boc-L-Glu-OBzl	D	Gly-OEt	Trt	$C_{45}H_{53}N_3O_8S$ amorphous	6	1.13(3H), 1.17(3H), 1.21(3H), 1.39(9H), 1.52-2.32(4H), 3.65(1H), 3.91(2H), 4:12(2H), 4.29(1H), 5.14(2H), 5.46(1H), 6.52(1H), 6.87(1H), 7.10-7.44(14H), 7.46-7.76(6H)
D-6	Boc-D-Glu-OMe	D	Gly-OEt	Trt	$C_{39}H_{49}N_3O_8S$ amorphous	6	1.12(3H), 1.20(3H), 1.25(3H), 1.42(9H), 1.48-2.36(4H), 3.63(1H), 3.68(3H), 3.94(2H), 4.17(2H), 4.30(1H), 5.34(1H), 6.26(1H), 6.48(1H), 7.15-7.34(9H), 7.57-7.67(6H)

Table 1 (continued)

D-7	Boc-L-Glu-(OBzl)	L	Gly-OEt	Trt	$C_{45}H_{53}N_3O_8S$ amorphous	6	1.12(3H), 1.15(3H), 1.24(3H), 1.40 (9H), 1.80-2.20(2H), 2.35-2.63 (2H), 3.51(1H), 3.92(2H), 4.10(1H), 4.15(2H), 5.10(2H), 5.34(1H), 6.34 (1H), 6.94(1H), 7.14-7.37(14H), 7.58-7.67(6H)
D-8	Boc-L-Asp-OBzl	D	Gly-OEt	Trt	$C_{44}H_{51}N_3O_8S$ amorphous	6	1.10(3H), 1.18(3H), 1.24(3H), 1.39 (9H), 2.62-2.96(2H), 3.51(1H), 3.90 (2H), 4.12(2H), 4.52(1H), 5.14(2H), 5.74(1H), 6.20-6.35(2H), 7.14-7.35 (14H), 7.56-7.66(6H)
D-9	Boc-L-Glu-OBzl	L	L-Ala-OEt	Trt	$C_{46}H_{55}N_3O_8S$ amorphous	6	1.09(3H), 1.15(3H), 1.23(3H), 1.34 (3H), 1.42(9H), 1.65-2.28(4H), 3.61 (1H), 4.14(2H), 4.33(1H), 4.44(1H), 5.12(2H), 5.38(1H), 6.24(1H), 6.38 (1H), 7.14-7.44(14H), 7.58-7.68(6H)
D-10	Boc-L-Glu-OBzl	L	L-Val-OMe	Trt	$C_{47}H_{57}N_3O_8S$ amorphous	6	0.85(3H), 0.89(3H), 1.12(3H), 1.21 (3H), 1.42(9H), 1.70-2.28(5H), 3.39(1H), 3.65(3H), 4.36(1H), 4.41 (1H), 5.09(2H), 5.46(1H), 6.19(1H), 6.46(1H), 7.15-7.41(14H), 7.59-7.69(6H)

Table 1 (continued)

D-11	Boc-L-Glu-OBzl	D	L-Val-OMe	Trt	$C_{47}H_{57}N_3O_8S$ amorphous	6	0.85(3H), 0.88(3H), 1.06(3H), 1.15 (3H), 1.39(9H), 1.60-2.37(5H), 3.68(3H), 3.76(1H), 4.26(1H), 4.44 (1H), 5.07-5.23(2H), 5.37(1H), 6.38 (1H), 6.49(1H), 7.15-7.44(14H), 7.56-7.66(6H)
D-12	Boc-L-Glu-OBzl	L	L-Leu-OEt	Trt	$C_{49}H_{61}N_3O_8S$ m.p. 177.0-179.0	6	0.85-0.97(6H), 1.10(3H), 1.18(3H), 1.22(3H), 1.42(9H), 1.30-2.27(7H), 3.61(1H), 4.11(2H), 4.34(1H), 4.44 (1H), 5.10(2H), 5.40(1H), 6.10(1H), 6.39(1H), 7.14-7.40(14H), 7.58-7.67(6H)
D-13	Boc-L-Glu-OBzl	L	L-Pro-OEt	Trt	$C_{47}H_{55}N_3O_8S$ amorphous	6	1.22(3H), 1.26(3H), 1.42(9H), 1.67 -2.34(8H), 3.06-3.20(1H), 3.40-3.52(1H), 3.63(3H), 3.93(1H), 4.37 (1H), 4.42(1H), 5.12(2H), 5.36(1H), 6.42(1H), 7.10-7.44(14H), 7.49-7.72(6H)

Table 1 (continued)

D-14	Boc-L-Glu(-OBzl)-	L	L-Phe-OEt	Trt	$C_{52}H_{59}N_3O_8S$ amorphous	6	1.08(3H), 1.13(3H), 1.26(3H), 1.42(9H), 1.54-2.24(4H), 3.02(2H), 3.39(1H), 4.12(2H), 4.32(1H), 4.75(1H), 5.12(2H), 5.46(1H), 6.20-6.38(2H), 7.03-7.38(19H), 7.53-7.63(6H)
D-15	Boc-L-Glu(-OBzl)-	L	SiMe$_3$ | L-Tyr-OEt	Trt	$C_{55}H_{67}N_3O_9SSi$ amorphous	6	0.26(9H), 1.09(3H), 1.15(6H), 1.43(9H), 1.58-2.30(4H), 2.95(2H), 3.33(1H), 4.06(2H), 4.33(1H), 4.70(1H), 5.12(2H), 5.49(1H), 6.23(1H), 6.32(1H), 6.75(2H), 6.97(2H), 7.10-7.40(14H), 7.55-7.65(6H)
D-16	Boc-L-Glu(-OBzl)-	L	(-OEt) L-Glu-OEt	Trt	$C_{50}H_{61}N_3O_{10}S$ m.p. 167.0-168.5	6	1.08(3H), 1.18(3H), 1.22(3H), 1.26(3H), 1.42(9H), 1.80-2.42(8H), 3.49(1H), 4.10(2H), 4.12(2H), 4.34(1H), 4.48(1H), 5.11(2H), 5.41(1H), 6.30(1H), 6.40(1H), 7.15-7.37(14H), 7.57-7.69(6H)

Table 1 (continued)

D-17	Boc-L-Glu-OBzl	L	$NHCHPh_2$	Trt	$C_{54}H_{57}N_3O_6S$ amorphous	6	1.07(3H), 1.16(3H), 1.41(9H), 1.68-2.23(4H), 3.89(1H), 4.31(1H), 5.10(2H), 5.36(1H), 6.09(1H), 6.28-6.43(2H), 7.10-7.36(24H), 7.50-7.58(6H)
D-18	Boc-L-Glu-OBzl	L	L-Asp(OBzl)-OBzl	Trt	$C_{59}H_{63}N_3O_{10}S$ amorphous	6	1.07(3H), 1.19(3H), 1.41(9H), 1.70-2.27(4H), 2.72-3.12(2H), 2.96(1H), 4.32(1H), 4.80(1H), 4.94-5.22(6H), 5.43(1H), 6.25(1H), 6.52(1H), 7.03-7.44(24H), 7.56-7.64(6H)
D-19	Boc-L-Glu-OBzl	L	L-Met-OEt	Trt	$C_{48}H_{59}N_3O_6S_2$ m.p. 161.5-163.0	6	1.11(3H), 1.21(3H), 1.23(3H), 1.43(9H), 1.72-2.28(6H), 2.05(3H), 2.47(2H), 3.38(1H), 4.15(2H), 4.34(1H), 4.56(1H), 4.97-5.23(2H), 5.42(1H), 6.25(1H), 6.39(1H), 7.14-7.37(14H), 7.58-7.67(6H)

Table 1 (continued)

D-20	Boc-L-Glu-OBzl	L	L-Ile-OMe	Trt	$C_{48}H_{59}N_3O_8S$ m.p. 159.5-160.5	6	0.76-0.96(6H), 1.00-1.59(2H), 1.11(3H), 1.20(3H), 1.43(9H), 1.71-2.30(5H), 3.43(1H), 3.65(3H), 4.36(1H), 4.44(1H), 4.95-5.22(2H), 5.44(1H), 6.28(1H), 6.45(1H), 7.08-7.42(14H), 7.52-7.76(6H)
D-21	Boc-L-Glu-OBzl	D	$NHCHPh_2$	Trt	$C_{54}H_{57}N_3O_8S$ amorphous	6	1.00(3H), 1.15(3H), 1.36(9H), 1.53-2.26(4H), 3.98(1H), 4.03(1H), 5.12(2H), 5.33(1H), 6.15(1H), 6.56(1H), 6.89(1H), 7.08-7.36(24H), 7.50-7.58(6H)
D-22	Boc-L-Glu-OBzl	D	L-Leu-OEt	Trt	$C_{49}H_{61}N_3O_8S$ amorphous	6	0.76-0.90(6H)), 1.09(3H), 1.54(3H), 1.22(3H), 1.30-2.32(7H), 1.39(9H), 3.67(1H), 4.11(2H), 4.24(1H), 4.50(1H), 5.14(2H), 5.32(1H), 6.30(1H), 6.40(1H), 7.14-7.37(14H), 7.55-7.64(6H)

Table 1 (continued)

D-23	Boc-L-Glu-OBzl	D	L-Phe-OEt	Trt	$C_{52}H_{59}N_3O_8S$ amorphous	6	1.02(3H), 1.12(6H), 1.40(9H), 1.60-2.29(4H), 3.03(2H), 3.62(1H), 4.06(2H), 4.24(1H), 4.73(1H), 5.14(2H), 5.36(1H), 6.31(1H), 6.54(1H), 7.06-7.40(19H), 7.65-7.64(6H)
D-24	Boc-L-Glu-OBzl	D	L-Glu(OEt)-OEt	Trt	$C_{50}H_{61}N_3O_{10}S$ amorphous	6	1.11(3H), 1.19(6H), 1.22(3H), 1.39(9H), 1.52-2.42(8H), 3.51(1H), 4.03(2H), 4.12(2H), 4.24(1H), 4.50(1H), 5.14(2H), 5.32(1H), 6.31(1H), 6.71(1H), 7.14-7.36(14H), 7.56-7.65(6H)
D-25	Boc-L-Glu-OBzl	L	Si(Me)$_3$ L-Ser-OMe	Trt	$C_{48}H_{61}N_3O_9SSi$ amorphous	6	0.04(9H), 1.15(3H), 1.16(3H), 1.42(9H), 1.60-2.26(4H), 3.48(1H), 3.65(3H), 3.86(1H), 4.00(1H), 4.31(1H), 4.54(1H), 5.11(2H), 5.40(1H), 6.32(1H), 6.58(1H), 7.13-7.36(14H), 7.59-7.69(6H)

Table 1 (continued)

D-26	Boc-L-Glu(OBzl)-	D	L-Pro-OMe	Trt	$C_{47}H_{55}N_3O_8S$ amorphous	6	0.97(6H), 1.39(9H), 1.63-2.50(8H), 3.44-3.68(1H), 3.64(3H), 3.71-3.85(1H), 4.28(1H), 4.42(1H), 4.77(1H), 5.15(2H), 5.36(1H), 6.39(1H), 7.12-7.36(14H), 7.50-7.62(6H)
D-27	Boc-L-Glu(OBzl)-	L	CH_2COOEt | Tyr-OEt	Trt	$C_{56}H_{65}N_3O_{11}S$ amorphous	6	1.08(3H), 1.15(3H), 1.17(3H), 1.30(3H), 1.42(9H), 1.63-2.28(4H), 2.97(2H), 3.39(1H), 4.76(2H), 4.27(2H), 4.32(1H), 4.59(2H), 4.71(1H), 5.12(2H), 5.46(1H), 6.23(1H), 6.31(1H), 6.81(2H), 7.03(2H), 7.10-7.42(14H), 7.54-7.66(6H)
D-28	Boc-L-Glu(OBzl)-	L	$SO_3 \cdot Bu_4N$ | DL-Phe-OH	Trt	$C_{66}H_{90}N_4O_{11}S_2$ amorphous	9	*0.72(3H), 0.80(3H), 0.94(12H), 1.22-2.40(20H), 1.36(9/2H), 1.37(9/2H), 2.80-3.50(10H), 4.04(1H), 4.39(1H), 4.50(1H), 5.12(2H), 7.09-8.07(28H)

Table 1 (continued)

D-29	Boc-L-Asp-OBzl	L	Gly-OEt	Trt	$C_{44}H_{51}N_3O_8S$ amorphous	6	1.09(3H), 1.19(3H), 1.27(3H), 1.41 (9H), 2.64-2.93(2H), 3.48(1H), 3.94 (2H), 4.17(2H), 4.55(1H), 5.12(2H), 5.66(1H), 6.14-6.33(2H), 7.10-7.32 (14H), 7.52-7.64(6H)
D-30	Boc-L-Glu-OBzl	L	OH	Trt	$C_{41}H_{46}N_2O_7S$ amorphous	3	1.08(3H), 1.18(3H), 1.42(9H), 1.83-2.32(4H), 3.63-3.72(1H), 4.34(1H), 5.12(2H), 5.39(1H), 6.49(1H), 7.10 -7.43(15H), 7.48-7.56(6H)
E-1	Boc	D	Gly-OH	Trt	$C_{31}H_{38}N_2O_5S$ amorphous	7	1.04(3H), 1.06(3H), 1.43(9H), 3.73 (1H), 4.00(2H), 5.69(2H), 6.68(1H), 7.10-7.33(9H), 7.54-7.64(6H), 8.28(1H)
E-2	Boc-L-Glu-OH	D	OH	Trt	$C_{34}H_{40}N_2O_7S$ amorphous	7	0.97(6H), 1.37(9H), 1.80-2.62(4H), 4.18-4.90(3H), 5.69(1H), 6.83(1H), 7.12-7.30(9H), 7.46-7.61(6H), 8.06(1H)

Table 1 (continued)

E-3	Boc-D-Glu-OH	D	OH	Trt	$C_{34}H_{40}N_2O_7S$ amorphous	7	0.96(6H), 1.36(9H), 1.82-2.53 (4H), 4.20-4.85(3H), 5.68(1H), 6.81(1H), 7.13-7.32(9H), 7.49-7.63(6H), 8.09(1H)
E-4	Ac	L	Gly-OH	Trt	$C_{28}H_{30}N_2O_4S$ amorphous	7	1.08(3H), 1.11(3H), 1.97(3H), 3.89(1H), 3.97(2H), 6.51(1H), 6.62(1H), 7.12-7.38(9H), 7.54-7.67(6H), 7.00-8.00(1H)
E-5	Boc-L-Glu-OH	L	Gly-OH	Trt	$C_{36}H_{43}N_3O_8S$ amorphous	7	0.89(3H), 0.97(3H), 1.45(9H), 1.71-2.80(4H), 3.47-3.70(2H), 4.20-4.73(2H), 5.07-5.50(2H), 7.06-7.27(9H), 7.47-7.64(6H), 8.05-9.00(3H)
E-6	Boc-L-Glu-OH	D	Gly-OH	Trt	$C_{36}H_{43}N_3O_8S$ amorphous	7	1.05(3H), 1.06(3H), 1.39(9H), 1.76-2.56(4H), 3.66-4.34(4H), 6.64 (1H), 6.00-8.16(19H)

Table 1 (continued)

E-7	Boc-D-Glu-OH	D	Gly-OH	Trt	$C_{36}H_{43}N_3O_8S$ amorphous	7	0.89(3H), 0.96(3H), 1.45(9H), 1.70-2.76(4H), 3.44-3.80(2H), 4.20-4.70(2H), 5.10-5.52(2H), 7.02-7.36(9H), 7.44-7.68(6H), 7.90-9.45(3H)
E-8	Boc-L-Glu-	L	Gly-OH	Trt	$C_{36}H_{43}N_3O_8S$ amorphous	7	*0.77(3H), 0.81(3H), 1.38(9H), 1.65-2.10(2H), 2.15-2.40(2H), 3.34(1H), 3.58-3.89(2H), 4.07 (1H), 4.40(1H), 6.80-7.88(16H), 7.77(1H), 8.42(1H), 12.28(1H)
E-9	Boc-L-Asp-OH	D	Gly-OH	Trt	$C_{35}H_{41}N_3O_8S$ amorphous	7	0.98(3H), 1.06(3H), 1.34(9H), 2.64-3.08(2H), 3.60-4.70(4H), 5.90(1H), 6.90-7.30(11H), 7.44 -7.66(6H), 9.54(2H)
E-10	Boc-L-Glu-OH	L	L-Ala-OH	Trt	$C_{37}H_{45}N_3O_8S$ amorphous	7	*0.78(3H), 0.82(3H), 1.26(3H), 1.39(9H), 1.60-2.54(4H), 3.33 (1H), 3.93(1H), 4.15(1H), 4.53 (1H), 7.04-7.38(10H), 7.49-7.59 (6H), 8.11(1H), 8.38(1H), 12.20 (1H)

Table 1 (continued)

E-11	Boc-L-Glu-OH	L	L-Val-OH	Trt	$C_{39}H_{49}N_3O_8S$ amorphous	7	0.86(3H), 0.89(3H), 1.02(3H), 1.06(3H), 1.41(9H), 1.80-2.55 (5H), 4.06(1H), 4.24-4.48(2H), 5.68(1H), 7.07-7.33(10H), 7.43 (1H), 7.53-7.65(6H), 8.50(2H)
E-12	Boc-L-Glu-OH	D	L-Val-OH	Trt	$C_{39}H_{49}N_3O_8S$ amorphous	7	0.87(3H), 0.90(3H), 1.04(3H), 1.08 (3H), 1.41(9H), 1.81-2.57(5H), 4.07(1H), 4.25-4.50(2H), 5.69(1H), 7.03-7.30(10H), 7.40(1H), 7.51-7.66(6H), 8.52(2H)
E-13	Boc-L-Glu-OH	L	L-Leu-OH	Trt	$C_{40}H_{51}N_3O_8S$ amorphous	7	*0.77-0.90(6H), 0.87(3H), 0.90 (3H), 1.39(9H), 1.30-2.12(5H), 2.36(2H), 3.68(1H), 3.94(1H), 4.22 (1H), 4.49(1H), 7.08-7.35(10H), 7.50-7.62(6H), 8.07(1H), 8.18(1H), 12.32(1H)
E-14	Boc-L-Glu-OH	L	L-Pro-OH	Trt	$C_{39}H_{47}N_3O_8S$ amorphous	7	*0.96(3H), 1.12(3H), 1.37(9H), 1.57-2.52(8H), 3.06-3.62(3H), 3.93(1H), 4.14(1H), 4.27(1H), 7.09 (1H), 7.10-7.38(9H), 7.44-7.62 (6H), 8.10(1H), 12.40(1H)

Table 1 (continued)

E-15	Boc-L-Glu-OH	L	L-Phe-OH	Trt	$C_{43}H_{49}N_3O_8S$ amorphous	7	*0.72(3H), 0.79(3H), 1.39(9H), 1.66-2.12(2H), 2.20-2.36(2H), 2.79-3.12(2H), 3.84-4.05(1H), 4.42(1H), 4.47(1H), 7.06-7.34 (15H), 7.48-7.60(6H), 7.97(1H), 8.32(1H), 12.50(2H)
E-16	Boc-L-Glu-OH	L	L-Tyr-OH	Trt	$C_{43}H_{49}N_3O_8S$ amorphous.	7	1.00(6H), 1.43(9H), 1.80-2.50(4H), 2.77-3.17(2H), 3.84(1H), 4.26(1H), 4.70(1H), 5.74(1H), 6.57(1H), 6.71 (2H), 6.83(1H), 6.94(2H), 7.09-7.38 (9H), 7.53-7.63(6H), 6.50-9.90(3H)
E-17	Boc-L-Glu-OH	L	L-Glu-OH	Trt	$C_{39}H_{47}N_3O_{10}S$ amorphous	7	0.99(3H), 1.09(3H), 1.43(9H), 1.85-2.64(8H), 3.91(1H), 4.23(1H), 4.49 (1H), 5.81(1H), 6.98(1H), 7.10-7.43 (10H), 7.52-7.74(6H), 8.20-11.6 (3H)
E-18	Boc-L-Glu-OH	L	$NHCHPh_2$	Trt	$C_{47}H_{51}N_3O_8S$ amorphous	7	1.06(6H), 1.40(9H), 1.70-2.50(4H), 4.12(1H), 4.26(1H), 5.48(1H), 6.06 (1H), 6.61(1H), 6.94-7.34(20H), 7.46-7.55(6H), 6.90-8.00(1H)

Table 1 (continued)

E-19	Boc-L-Glu-OH	L	L-Asp-OH	Trt	$C_{38}H_{45}N_3O_{10}S$ amorphous	7	*0.79(3H), 0.82(3H), 1.39(9H), 1.60-2.78(6H), 3.36(1H), 3.95(1H), 4.40-4.58(2H), 7.08-7.38(10H), 7.49-7.60(6H), 8.11(1H), 8.37(1H), 12.51(2H)
E-20	Boc-L-Glu-OH	L	L-Met-OH	Trt	$C_{39}H_{49}N_3O_8S_2$ amorphous	7	*0.78(3H), 0.82(3H), 1.38(9H), 1.64-2.60(8H), 2.00(3H), 3.33(1H), 3.95(1H), 4.28(1H), 4.50(1H), 7.10-7.36(10H), 7.50-7.60(6H), 8.10(1H), 8.30(1H), 12.52(1H)
E-21	Boc-L-Glu-OH	L	L-Ile-OH	Trt	$C_{40}H_{51}N_3O_8S$ amorphous	7	*0.70-0.90(12H), 1.02-1.54(2H), 1.38(9H), 1.66-2.10(3H), 2.22-2.42(2H), 3.32(1H), 3.93(1H), 4.11(1H), 4.54(1H), 7.11-7.37(10H), 7.48-7.60(6H), 8.00(1H), 8.08(1H), 12.42(1H)

Table 1 (continued)

E-22	Boc-L-Glu-OH	D	$NHCHPh_2$	Trt	$C_{47}H_{51}N_3O_8S$ m.p. 125.5-127.0	7	1.05(3H), 1.15(3H), 1.38(9H), 1.67-2.38(4H), 3.90(1H), 4.01(1H), 5.46(1H), 6.13(1H), 6.84(1H), 7.00-7.30(21H), 7.46-7.58(6H)
E-23	Boc-L-Glu-OH	D	L-Leu-OH	Trt	$C_{40}H_{51}N_3O_8S$ amorphous	7	*0.63-0.92(12H), 1.25-2.03(5H), 1.38(9H), 2.14-2.56(2H), 3.34(1H), 3.88(1H), 4.22(1H), 4.54(1H), 7.04(1H), 7.15-7.36(9H), 7.47-7.59(6H), 8.14(1H), 8.42(1H), 12.44(1H)
E-24	Boc-L-Glu-OH	D	L-Phe-OH	Trt	$C_{43}H_{49}N_3O_8S$ amorphous	7	*0.59(6H), 1.39(9H), 1.78-2.10(2H), 2.20-2.55(2H), 2.79-3.11(2H), 3.37(1H), 3.94(1H), 4.31-4.51(2H), 7.06-7.37(15H), 7.43-7.56(6H), 8.02(1H), 8.37(1H), 12.60(1H)

Table 1 (continued)

E-25	Boc-L-Glu-OH	D	L-Glu-OH	Trt	$C_{39}H_{47}N_3O_{10}S$ amorphous	7	*0.74(3H), 0.80(3H), 1.39(9H), 1.62-2.08(4H), 2.12-2.54(4H), 3.35(1H), 3.88(1H), 4.24(1H), 4.53(1H), 7.04(1H), 7.11-7.37(9H), 7.47-7.60(6H), 8.02(1H), 8.46(1H), 12.34(2H)
E-26	Boc-L-Glu-OH	L	L-Ser-OH	Trt	$C_{37}H_{45}N_3O_9S$ amorphous	7	*0.80(3H), 0.85(3H), 1.39(9H), 1.62-2.12(2H), 2.22-2.53(2H), 3.34(2H), 3.56-3.77(2H), 3.93(1H), 4.24(1H), 4.54(1H), 7.06-7.35(10H), 7.48-7.61(6H), 8.10(1H), 8.19(1H), 12.44(1H)
E-27	Boc-L-Glu-OH	D	L-Pro-OH	Trt	$C_{39}H_{47}N_3O_8S$ amorphous	7	*0.85(3H), 0.88(3H), 1.38(9H), 1.65-2.46(8H), 3.33(1H), 3.30-3.70(2H), 3.75-3.97(1H), 4.20(1H), 4.80(1H), 6.99(1H), 7.14-7.17(9H), 7.43-7.55(6H), 8.17(1H), 12.42(1H)

Table 1 (continued)

E-28	Boc-L-Glu-OH	L	$\overset{CH_2COOH}{\underset{|}{}}$ Tyr-OH	Trt	$C_{45}H_{51}N_3O_{11}S$ amorphous	7	*0.75(3H), 0.81(3H), 1.39(9H), 1.60-2.14(2H), 2.21-2.46(2H), 2.75-3.02(2H), 3.35(1H), 3.98(1H), 4.37(1H), 4.48(1H), 4.60(2H), 6.75 (2H), 7.04-7.38(12H), 7.50-7.62 (6H), 8.03(1H), 8.27(1H), 12.67(2H)
E-29	Boc-L-Glu-OH	L	$\overset{SO_3\cdot Bu_4N}{\underset{|}{}}$ DL-Phe-OH	Trt	$C_{59}H_{84}N_4O_{11}S_2$ amorphous	7	*0.76(3H), 0.82(3H), 0.94(12H), 1.20-1.42(8H), 1.38(9H), 1.47-1.68 (8H), 1.72-2.15(2H), 2.20-2.41(2H) , 2.80-3.30(11H), 3.94(1H), 4.41 (1H), 4.49(1H), 7.07-7.38(11H), 7.43-7.66(9H), 8.04(1H), 8.28(1H), 12.45(1H),
E-30	Boc-L-Asp-OH	L	Gly-OH	Trt	$C_{39}H_{41}N_3O_8S$ amorphous	7	1.12(3H), 1.15(3H), 1.28(9H), 2.62-3.05(2H), 3.72-4.32(3H), 4.51(1H), 5.93(1H), 6.38-7.39 (11H), 7.53-7.64(6H), 9.63(2H)

Table 1 (continued)

E-31	Boc-L-Glu-OH	L	OH	Trt	$C_{34}H_{40}N_2O_7S$ amorphous	7	*0.85(3H), 0.89(3H), 1.38(9H), 1.62-2.11(2H), 2.23-2.38(2H), 3.40(1H), 3.91(1H), 4.11(1H), 7.03(1H), 7.14-7.36(9H), 7.47-7.57(6H), 8.03(1H), 12.52(1H)
E-32	Boc	L	Gly-OH	Trt	$C_{31}H_{36}N_2O_5S_2$ amorphous	7	1.04(3H), 1.06(3H), 1.43(9H) 3.74(1H), 4.00(2H), 5.63(1H), 6.65(1H), 7.10-7.35(9H), 7.53-7.61(6H), 8.63(1H)
F-1	H	D	Gly-OH	H	$C_7H_{14}N_2O_3S \cdot HCl$ 49-54℃ decomp.	8	**1.42(3H), 1.49(3H), 3.98(2H), 3.99(1H)
F-2	H-L-Glu-OH	D	OH	H	$C_{10}H_{18}N_2O_5S \cdot HCl$ 84-89℃ decomp.	8	**1.38(3H), 1.43(3H), 2.01-2.22(2H), 2.45-2.59(2H), 3.93(1H), 4.43(1H)
F-3	H-D-Glu-OH	D	OH	H	$C_{10}H_{18}N_2O_5S \cdot HCl$ 89-93℃ decomp.	8	**1.37(3H), 1.42(3H), 2.08-2.22(2H), 2.49-2.60(2H), 3.97(1H), 4.41(1H)

Table 1 (continued)

F-4	Ac	L	Gly-OH	H	$C_9H_{16}N_2O_4S$ 65-72℃ decomp.	8	**1.35(3H), 1.42(3H), 2.01(3H), 3.94(2H), 4.37(1H)
F-5	H-L-Glu-OH	L	Gly-OH	H	$C_{12}H_{21}N_3O_8S \cdot HCl$ 121-125℃ decomp.	8	**1.35(3H), 1.41(3H), 2.06-2.21 (2H), 2.41-2.69(2H), 3.93(2H), 3.97 (1H), 4.38(1H)
F-6	H-L-Glu-OH	D	Gly-OH	H	$C_{12}H_{21}N_3O_8S \cdot HCl$ 113-117℃ decomp.	8	**1.37(3H), 1.42(3H), 2.03-2.23 (2H), 2.43-2.60(2H), 3.94(3H), 4.41(1H)
F-7	H-D-Glu-OH	D	Gly-OH	H	$C_{12}H_{21}N_3O_8S \cdot HCl$ 127-131℃ decomp.	8	**1.35(3H), 1.41(3H), 2.07-2.21 (2H), 2.41-2.67(2H), 3.93(2H), 3.96(1H), 4.38(1H)
F-8	H-L-Glu-	L	Gly-OH	H	$C_{12}H_{21}N_3O_8S \cdot HCl$ 129-135℃ decomp.	8	**1.37(3H), 1.42(3H), 2.04-2.27 (2H), 2.40-2.54(2H), 3.94(2H), 4.18 (1H), 4.47(1H)
F-9	H-L-Asp-OH	D	Gly-OH	H	$C_{11}H_{19}N_3O_8S \cdot HCl$ 130-134℃ decomp.	8	**1.35(3H), 1.40(3H), 2.89-3.17 (2H), 3.92(2H), 4.26(1H), 4.39(1H)

Table 1 (continued)

F-10	H-L-Glu-OH	L	L-Ala-OH	H	$C_{13}H_{24}N_3O_6S \cdot HCl$ 125-128℃ decomp.	8	**1.35(6H), 1.40(3H), 2.06-2.21 (2H), 2.40-2.66(2H), 3.97(1H), 4.28 (1H), 4.37(1H)
F-11	H-L-Glu-OH	L	L-Val-OH	H	$C_{15}H_{27}N_3O_6S \cdot HCl$ 128-133℃ decomp.	8	**0.87(3H), 0.90(3H), 1.36(3H), 1.40 (3H), 1.98-2.30(3H), 2.38-2.70(2H), 3.98(1H), 4.13-4.23(1H), 4.46(1H)
F-12	H-L-Glu-OH	D	L-Val-OH	H	$C_{15}H_{27}N_3O_6S \cdot HCl$ 119-124℃ decomp.	8	**0.89(3H), 0.92(3H), 1.34(3H), 1.39 (3H), 1.96-2.31(3H), 2.42-2.61(2H), 3.95(1H), 4.07-4.20(1H), 4.92(1H)
F-13	H-L-Glu-OH	L	L-Leu-OH	H	$C_{16}H_{29}N_3O_6S \cdot HCl$ 114-119℃ decomp.	8	**0.78(3H), 0.84(3H), 1.35(3H), 1.40(3H), 1.53-1.72(3H), 2.03-2.17 (2H), 2.46-2.58(2H), 3.92(1H), 4.34 (1H), 4.38(1H)
F-14	H-L-Glu-OH	L	L-Pro-OH	H	$C_{15}H_{25}N_3O_6S \cdot HCl$ 148-152℃ decomp.	8	**1.39(3H), 1.41(3H), 1.86-2.67 (8H), 3.80(2H), 3.97(1H), 4.35(1H) 4.60-4.80(1H)

Table 1 (continued)

F-15	H-L-Glu-OH	L	L-Phe-OH	H	$C_{19}H_{27}N_3O_6S \cdot HCl$ 119-125℃ decomp.	8	**1.24(3H), 1.26(3H), 1.96-2.24 (2H), 2.28-2.58(2H), 2.82-3.29(2H), 3.97(1H), 4.30(1H), 4.69(1H), 7.13-7.32(5H)
F-16	H-L-Glu-OH	L	L-Tyr-OH	H	$C_{19}H_{27}N_3O_7S \cdot HCl$ 133-139℃ decomp.	8	**1.24(3H), 1.26(3H), 1.98-2.24 (2H), 2.29-2.61(2H), 2.74-3.26(2H), 3.94(1H), 4.30(1H), 4.69(1H), 6.72 (2H), 7.05(2H)
F-17	H-L-Glu-OH	L	L-Glu-OH	H	$C_{15}H_{25}N_3O_4S \cdot HCl$ 140-150℃ decomp.	** 8	1.38(3H), 1.42(3H), 1.83-2.30(4H) 2.39-2.65(4H), 3.95(1H), 4.40(1H), 4.42(1H)
F-18	H-L-Glu-OH	L	$NHCHPh_2$	H	$C_{23}H_{29}N_3O_4S \cdot HCl$ 140-147℃ decomp.	8	*1.29(3H), 1.33(3H), 1.85-2.67(2H), 3.40(1H), 3.86(1H), 4.70(1H), 6.12 (1H), 7.12-7.43(10H), 8.20(1H), 8.50(1H), 9.13(1H)
F-19	H-L-Glu-OH	L	L-Asp-OH	H	$C_{14}H_{22}N_3O_8S \cdot HCl$ 128-133℃ decomp.	8	**1.39(3H), 1.44(3H), 2.10-2.23 (2H), 2.51-2.62(2H), 2.94(2H), 3.97 (1H), 4.41(1H)

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Table 1 (continued)

F-20	H-L-Glu-OH	L	L-Met-OH	H	$C_{15}H_{28}N_3O_6S_2 \cdot HCl$ 115-119℃decomp.	8	**1.39(3H), 1.44(3H), 1.93-2.28 (4H), 2.04(3H), 2.41-2.70(4H), 4.00 (1H), 4.40(1H), 4.54(1H)
F-21	H-L-Glu-OH	L	L-Ile-OH	H	$C_{16}H_{29}N_3O_6S \cdot HCl$ 121-126℃ decomp.	8	**0.83(3H), 0.89(3H), 1.05-1.56 (2H), 1.38(3H), 1.42(3H), 1.76-1.96 (1H), 2.06-2.30(2H), 2.43-2.72(2H), 4.01(1H), 4.25(1H), 4.47(1H)
F-22	H-L-Glu-OH	D	$NHCHPh_2$	H	$C_{23}H_{29}N_3O_4S \cdot HCl$ 120-125℃ decomp.	8	*1.30(3H), 1.35(3H), 1.96-2.15 (2H), 2.36-2.57(2H), 2.80(1H), 3.55 (2H), 3.85(1H), 4.72(1H), 6.14(1H), 7.12-7.48(10H), 8.19(1H), 8.49(2H), 9.12(1H)
F-23	H-L-Glu-OH	D	L-Leu-OH	H	$C_{16}H_{29}N_3O_6S \cdot HCl$ 125-129℃ decomp.	8	**0.70-0.79(6H), 1.36(3H), 1.41 (3H), 1.50-1.82(3H), 2.06-2.31(2H), 2.42-2.68(2H), 4.01(1H), 4.33(1H), 4.43(1H)

Table 1 (continued)

F-24	H-L-Glu-OH	D	L-Phe-OH	H	$C_{19}H_{27}N_3O_6S \cdot HCl$ 126-129℃ decomp.	8	*1.13(3H), 1.18(3H), [illegible]0-2.13(2H), 2.41-2.66(2H), 2.53([illegible]), 2.41-2.58(2H), 3.60(1H), 3.86([illegible]), 3.45(1H), 4.51(1H), 7.11-7.40([illegible]), 8.12(1H), 8.20-8.80(3H), 12.50([illegible]1)
F-25	H-L-Glu-OH	D	L-Glu-OH	H	$C_{15}H_{25}N_3O_4S \cdot HCl$ 120-123℃ decomp.	8	*1.33(3H), 1.37(3H), [illegible].65-2.13(4H), 2.26-2.39(2H), 2.40-2.57(2H), 2.79(1H), 3.46(3H), 3.88(1H), 4.23(1H), 4.61(1H), 8.14(1H), 8.41(2H), 8.48(1H), 12.10(1H)
F-26	H-L-Glu-OH	L	L-Ser-OH	H	$C_{13}H_{23}N_3O_7S \cdot HCl$ 115-119℃ decomp.	8	*1.40(6H), 1.88-2.20(2H), 2.26-2.64(2H), 2.79(1H), 3.40(2H), 3.58(3H), 3.86(1H), 4.25(1H), 4.65(1H), 8.11(1H), 8.20-8.44(3H), 12.65(1H)
F-27	H-L-Glu-OH	D	L-Pro-OH	H	$C_{15}H_{25}N_3O_6S \cdot HCl$ 137-142℃ decomp.	8	*1.33(3H), 1.38(3H), 1.76-2.24(6H), 2.30-2.60(2H), 2.93(1H), 3.50(2H), 3.60-3.95(3H), 4.21-4.30(1H), 4.92(1H), 8.22-8.62(3H), 12.50(1H)

Table 1 (continued)

F-28	H-L-Glu-OH	L	L-Tyr-OH (CH_2COOH)	H	$C_{21}H_{29}N_3O_9S \cdot HCl$ 120-124℃ decomp.	8	**1.26(6H), 2.01-2.19(2H), 2.34-2.62(2H), 2.80-2.96(1H), 3.12-3.25(1H), 3.97(1H), 4.32(1H), 4.66(3H), 6.85(2H), 7.15(2H)
F-29	H-L-Glu-OH	L	DL-Phe-OH (SO_3H)	H	$C_{19}H_{27}N_3O_9S_2 \cdot HCl$ 216-220℃ decomp.	8	*1.32(6H), 1.86-2.03(2H), 2.24-2.40(2H), 2.63(1H), 3.05-3.22(2H), 3.78(4H), 3.96(1H), 4.46-4.61(2H), 7.15-7.28(2H), 7.42-7.61(2H), 7.86(1H), 8.26-8.58(3H)
F-30	H-L-Asp-OH	L	Gly-OH	H	$C_{13}H_{19}N_3O_8S \cdot HCl$ 146-149℃ decomp.	8	**1.39(3H), 1.45(3H), 2.94-3.21(2H), 3.98(2H), 4.26(1H), 4.45(1H)
F-31	H-L-Glu-OH	L	OH	H	$C_{10}H_{18}N_2O_5S \cdot HCl$ 52- 55℃ decomp.	8	**1.38(3H), 1.44(3H), 2.10-2.24(2H), 2.53-2.62(2H), 4.01(1H), 4.43(1H)

Table 1 (continued)

F-32	H	L	Gly-OH	H	$C_7H_{14}N_2O_3S \cdot HCl$ 57.5-59℃ decomp.	8	**1.46(3H), 1.54(3H), 4.01(3H)

Compounds F-1 to F-3 and F-32 were isolated as respective hydrochlorides.

* ; measured in DMSO-d_6

** ; measured in D_2O

Working Example 1 (Synthesis of the Compound 8)

To the solution of (N-γ-L-glutamyl-D-penicillamyl)glycine hydrochloride (F-5) (0.3 g) in 1N-hydrochloric acid (0.81 ml) and methanol (1.6 ml), was added dropwise at room temperature the solution of sodium nitrite (0.11 g) in water (0.5 ml). After stirring at room temperature for 30 minutes, methanol was evaporated off under reduced pressure, and the solid precipitated by addition of acetone to the residue which was washed with acetone, to give (N-γ-L-glutamyl-S-nitroso-D-penicillamyl)glycine (0.19 g).

Working Example 2 (Synthesis of the Compound 7)

To the solution of (N-γ-L-glutamyl-D-penicillamyl)glycine hydrochloride (0.5 g) in methanol (5 ml), was added at 0°C the solution of ethyl nitrite in ethanol (10%) (1.1 ml). At the same temperature a drop of 4N-hydrochloric acid-methanol solution was added, and the mixture was stirred for 30 minutes. The solvent was evaporated off under reduced pressure, and the resultant crystals were washed with diethyl ether, to give (N-γ-L-glutamyl-S-nitroso-L-penicillamyl)glycine hydrochloride (0.5 g).

In the same way, the Compounds 1 to 6, 9 to 11, and 13 to 34 listed in Table 2 shown below were synthesized.

Working Example 3 (Synthesis of the Compound 12)

To the solution of (N-β-L-aspartyl-D-penicillamyl)glycine hydrochloride (0.2 g) in 1N-hydrochloric acid (0.56 ml) and water (1.0 ml), was added dropwise at room temperature the solution of sodium nitrite (0.077 g) in water (0.5 ml). The reaction mixture was stirred at room temperature for 30 minutes, loaded onto an LH-20 column, and eluted with water. The fractions containing the desired product were freeze-dried, to give (N-β-L-asparagyl-S-nitroso-D-penicillamyl)glycine (0.2 g).

Table 2 shows the structure, physical properties, and NMR data of the Compounds 1 to 34 obtained in the Working Examples.

Table 2

Compound	Configuration X	Configuration of Pen	Configuration Y	Molecular formula Physical properties	Related Ex. No.	NMR spectra (δ, ppm) in D_2O	IR (KBr) (cm^{-1}) others
1	H	D	Gly-OH	$C_7H_{13}N_3O_4S \cdot HCl$ 44-48℃ decomp.	2	1.93(3H), 2.11(3H), 4.02 (2H), 4.81(1H)	3800-2350, 1735, 1681, 1550-1510, 1400, 1380, 1320, 1215, 1130, 1040, 1015, 660
2	H-L-Glu-OH	D	OH	$C_{10}H_{17}N_3O_6S \cdot HCl$ amorphous	2	1.91(3H), 1.94(3H), 1.96 -2.24(2H), 2.34-2.61 (2H), 3.92(1H), 5.19(1H)	3700-2200, 1733, 1655, 1515, 1395, 1375, 1220, 1126, 990, 663
3	H-D-Glu-OH	D	OH	$C_{10}H_{17}N_3O_6S \cdot HCl$ 68-75℃ decomp.	2	1.91(3H), 1.94(3H), 2.02 -2.16(2H), 2.40-2.53 (2H), 3.94(1H), 5.17(1H)	3800-2200, 1735, 1650, 1515, 1395, 1375, 1220, 1128, 990, 665

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Table 2 (continued)

4	Ac	L	Gly-OH	$C_9H_{15}N_3O_5S$ amorphous	2	1.89(3H), 1.92(3H), 1.97 (3H), 3.87-3.98(2H), 5.16(1H)	3700-2250, 1740, 1655, 1520, 1375, 1215, 1135, 1035, 665
5	H-L-Glu-OH	L	Gly-OH	$C_{12}H_{20}N_4O_7S \cdot HCl$ 84-89℃decomp.	2	1.88(3H), 1.98(3H), 1.90 -2.22(2H), 2.30-2.67 (2H), 3.81-3.99(3H), 5.21(1H)	3800-2150, 1738, 1650, 1525, 1415, 1392, 1371, 1215, 1130, 1035, 665
6	H-L-Glu-OH	D	Gly-OH	$C_{12}H_{20}N_4O_7S$ amorphous	1	1.90(3H), 1.99(3H), 1.90 -2.13(2H), 2.26-2.65 (2H), 3.67(1H), 3.77(2H) 5.21(1H)	3700-2400, 1640, 1520, 1392, 1232 UV(H_2O): λmax= 340.0nm
7	H-L-Glu-OH	D	Gly-OH	$C_{12}H_{20}N_4O_7S \cdot HCl$ 108-113℃ decomp.	2	1.89(3H), 1.98(3H), 1.90 -2.16(2H), 2.40-2.56 (2H), 3.91(1H), 3.93(2H) 5.20(1H)	3800-2200, 1738, 1650, 1525, 1415, 1395, 1371, 1220, 1132, 1034, 665

Table 2 (continued)

8	H-D-Glu-OH	D	Gly-OH	$C_{12}H_{20}N_4O_7S \cdot HCl$ 100-105℃ decomp.	2	1.90(3H), 1.99(3H), 1.90-2.17(2H), 2.36-2.60(2H), 3.91(1H), 3.94(2H) 5.21(1H)	3800-2200, 1650, 1520, 1395, 1313, 1235, 1130, 665
9	H-L-Glu-	L	Gly-OH	$C_{12}H_{20}N_4O_7S \cdot HCl$ 98-105℃ decomp.	2	1.91(3H), 2.01(3H), 2.00-2.24(2H), 2.30-2.60(2H), 3.95(2H), 4.09(1H) 5.27(1H)	3700-2300, 1720, 1660, 1540, 1500, 1410, 1210, 665
10	H-L-Asp-OH	D	Gly-OH	$C_{11}H_{18}N_3O_6S$ amorphous	3	1.93(3H), 2.01(3H), 2.69-3.06(2H), 3.92-4.02(3H), 5.24(1H)	3700-2300, 1738, 1658, 1526, 1385, 1218 UV(H_2O): λmax= 336.8nm
11	H-L-Asp-OH	D	Gly-OH	$C_{11}H_{18}N_3O_6S \cdot HCl$ 95-100℃ decomp.	2	1.87(3H), 1.96(3H), 2.80-3.09(2H), 3.80-4.04(2H), 4.27(1H), 5.18(1H)	3700-2200, 1736, 1653, 1535, 1210, 665

Table 2 (continued)

12	H-L-Glu-OH	L	L-Ala-OH	$C_{13}H_{22}N_4O_7S \cdot HCl$ 107-112℃ decomp.	2	1.37(3H), 1.91(3H), 2.01 (3H), 1.90-2.17(2H), 2.39-2.55(2H), 3.92(1H) 4.23-4.38(1H), 5.18(1H)	3700-2200, 1730, 1650, 1520, 1455, 1390, 1370, 1218, 1150, 835, 665
13	H-L-Glu-OH	L	L-Val-OH	$C_{15}H_{26}N_4O_7S \cdot HCl$ 118-122℃ decomp.	2	0.86(3H), 0.89(3H), 1.89 (3H), 1.98(3H), 0.80-2.23(3H), 2.37-2.58(2H) 3.91(1H), 4.12-4.23(1H) 5.25(1H)	3700-2250, 1725, 1650, 1520, 1394, 1372, 1220, 1145, 1128, 665
14	H-L-Glu-OH	D	L-Val-OH	$C_{15}H_{26}N_4O_7S \cdot HCl$ 112-117℃ decomp.	2	0.87(3H), 0.91(3H), 1.90 (3H), 1.96(3H), 1.95-2.23(3H), 2.34-2.54 (2H), 3.90(1H), 4.07-4.26(1H), 5.30(1H)	3700-2250, 1738, 1650, 1522, 1392, 1370, 1220, 1145, 668
15	H-L-Glu-OH	L	L-Leu-OH	$C_{16}H_{28}N_4O_7S \cdot HCl$ 120-124℃ decomp.	2	0.70-0.92(6H), 1.46-1.73(3H), 1.79-2.19 (2H), 1.89(3H), 1.97(3H) 2.35-2.60(2H), 3.89(1H) 4.25-4.40(1H), 5.17(1H)	3700-2200, 1725, 1645, 1520, 1390, 1370, 1225, 1210, 1150, 665

Table 2 (continued)

16	H-L-Glu-OH	L	L-Pro-OH	$C_{15}H_{24}N_4O_7S \cdot HCl$ 120-125℃ decomp.	2	1.87(3H), 2.02(3H), 1.64-2.52(8H), 3.68-3.93(3H), 3.86(1H), 5.56(1H)	3650-2200, 1740, 1625, 1505, 1450, 1210, 1190, 665
17	H-L-Glu-OH	L	L-Phe-OH	$C_{19}H_{26}N_4O_7S \cdot HCl$ 122-127℃ decomp.	2	1.74(3H), 1.87(3H), 1.90-2.19(2H), 2.21-2.50(2H), 2.75-2.98(1H), 3.08-3.28(1H), 3.89(1H) 4.55-4.70(1H), 5.10(1H) 7.06-7.40(5H)	3800-2200, 1730, 1650, 1520, 1459, 1395, 1374, 1225, 1132, 703
18	H-L-Glu-OH	L	L-Tyr-OH	$C_{19}H_{26}N_4O_8S \cdot HCl$ 107-112℃ decomp.	2	1.76(3H), 1.86(3H), 1.94-2.14(2H), 2.20-2.46(2H), 2.77(1H), 3.15(1H) 3.87(1H), 4.55-4.70(1H) 5.08(1H), 6.70(2H), 7.03(1H)	3800-2200, 1730, 1650, 1518, 1450, 1395, 1375, 1230, 1130, 1110, 835, 670

Table 2 (continued)

19	H-L-Glu-OH	L	L-Glu-OH	$C_{15}H_{24}N_4O_9S \cdot HCl$ 80-85℃decomp.	2	1.88(3H), 1.97(3H), 1.70-2.50(8H), 3.90(1H), 4.39(1H), 5.17(1H)	3800-2230, 1730, 1655, 1520, 1455, 1395, 1375, 1220, 1135, 665
20	H-L-Glu-OH	L	$NHCHPh_2$	$C_{23}H_{28}N_4O_5S \cdot HCl$ 120-130℃ decomp.	2	*1.91(3H), 1.96(3H), 2.20-2.57(4H), 3.40(1H), 3.82(1H), 5.46(1H), 6.18(1H), 7.18-7.40(10H), 8.40(3H), 8.62(1H), 9.51(1H)	3700-2150, 1740, 1650, 1520, 1458, 1393, 1372, 1232, 1125, 1032, 702
21	H-L-Glu-OH	L	L-Asp-OH	$C_{14}H_{21}N_4O_9S \cdot HCl$ 84- 88℃ decomp.	2	1.92(3H), 2.00(3H), 2.02-2.19(2H), 2.42-2.55(2H), 2.86-2.96(2H), 3.93(1H), 4.72(1H), 5.20(1H)	3700-2200, 1735, 1650, 1525, 1225, 670
22	H-L-Glu-OH	L	L-Met-OH	$C_{15}H_{25}N_4O_7S \cdot HCl$ 104-109℃ decomp.	2	1.82-2.26(4H), 1.92(3H), 2.01(3H), 2.03(3H), 2.37-2.66(4H), 3.95(1H), 4.54(1H), 5.20(1H)	3700-2200, 1735, 1650, 1520, 1225, 670

Table 2 (continued)

23	H-L-Glu-OH	L	L-Ile-OH	$C_{16}H_{28}N_4O_7S \cdot HCl$ 109-115℃ decomp.	2	0.82(3H), 0.88(3H), 1.22 (1H), 1.27-1.53(1H), 1.77-2.24(3H), 1.91(3H), 1.99(3H), 2.41-2.53 (2H), 3.94(1H), 4.24 (1H), 5.25(1H)	3700-2200, 1730, 1650, 1520, 1220, 670
24	H-L-Glu-OH	D	$NHCHPh_2$	$C_{23}H_{28}N_4O_5S \cdot HCl$ 150-155℃ decomp.	2	*1.80-2.20(2H), 1.91 (3H), 1.96(3H), 2.26-2.44(2H), 3.60(1H), 3.81 (1H), 5.45(1H), 6.17(1H), 7.20-7.43(10H), 8.32 (3H), 8.56(1H). 9.49(1H)	3700-2200, 1735, 1645, 1520, 1230, 700
25	H-L-Glu-OH	D	L-Leu-OH	$C_{16}H_{28}N_4O_7S \cdot HCl$ 130-136℃ decomp.	2	0.75-1.01(6H), 1.45-1.76(3H), 1.92(3H), 1.96 (3H), 2.06-2.20(2H), 2.43-2.61(2H), 3.95(1H), 4.30(1H), 5.27(1H)	3700-2200, 1730, 1645, 1520, 1390, 1370, 1225, 665

Table 2 (continued)

26	H-L-Glu-OH	D	L-Phe-OH	$C_{19}H_{25}N_4O_7S \cdot HCl$ 120-125℃ decomp.	2	1.63(6H), 1.89-2.25 (2H), 2.30-2.66(2H), 2.94(1H), 3.18-3.43 (1H), 3.91(1H), 4.63-4.70(1H), 5.12(1H), 7.05-7.50(5H)	3700-2200, 1730, 1650, 1520, 1455, 1390, 1370, 1220, 1125, 700, 665
27	H-L-Glu-OH	D	L-Glu-OH	$C_{15}H_{24}N_4O_9S \cdot HCl$ 91- 96℃ decomp.	2	0.80-2.27(4H), 1.92 (3H), 1.97(3H), 2.34-2.64(4H), 3.95(1H), 4.34(1H), 5.25(1H)	3700-2200, 1730, 1650, 1520, 1220, 665
28	H-L-Glu-OH	L	L-Ser-OH	$C_{13}H_{23}N_4O_8S \cdot HCl$ 89- 92℃ decomp.	2	1.94(3H), 2.03(3H), 2.05-2.22(2H), 2.42-2.55(2H), 3.79-4.02 (3H), 4.52(1H), 5.29(1H)	3800-2200, 1735, 1650, 1520, 1390, 1370, 1225, 1135, 1070, 665
29	H-L-Glu-OH	D	L-Pro-OH	$C_{15}H_{24}N_4O_7S \cdot HCl$ 77- 81℃ decomp.	2	1.87(3H), 1.90-2.36 (6H), 2.01(3H), 2.43-2.57(2H), 3.68-3.89 (2H), 3.96(1H), 4.32 (1H), 5.64(1H)	3700-2200, 1735, 1630, 1510, 1450, 1220, 1190, 665

Table 2 (continued)

30	H-L-Glu-OH	L	L-Tyr-OH	$C_{21}H_{28}N_4O_{10}S\cdot HCl$ 108-112℃ decomp.	2	1.77(3H), 1.87(3H), 1.96-2.12(2H), 2.31-2.43(2H), 2.76-2.92(1H), 3.10-3.26(1H), 3.90(1H), 4.51-4.70(1H), 4.64(2H), 5.11(1H), 6.82(2H), 7.13(2H)	3700-2200, 1735, 1650, 1515, 1220, 835, 670
31	H-L-Glu-OH	L	DL-Phe-OH	$C_{19}H_{26}N_4O_{10}S_2\cdot HCl$ 140-145℃ decomp.	2	1.79(3H), 1.89(3H), 1.95-2.21(2H), 2.31-2.43(2H), 2.82-2.97(1H), 3.06-3.19(1H), 3.93(1H), 4.52-4.73(1H), 5.13(1H), 7.28-7.43(2H), 7.59-7.78(2H)	3700-2200, 1735, 1655, 1520, 1215, 1180, 1120, 1035, 1005, 680
32	H-L-Asp-OH	L	Gly-OH	$C_{11}H_{18}N_4O_7S\cdot HCl$ 85- 90℃ decomp.	2	1.91(3H), 2.00(3H), 2.87-3.14(2H), 3.97(2H), 4.24(1H), 5.24(1H)	3750-2200, 1740, 1655, 1535, 1410, 1390, 1210, 1130, 660

Table 2 (continued)

33	H-L-Glu-OH	L	OH	$C_{10}H_{17}N_3O_6S \cdot HCl$ 73- 80℃ decomp.	2	1.93(3H), 1.96(3H), 2.06-2.18(2H), 2.44-2.55(2H), 3.98(1H), 5.19(1H)	3800-2200, 1735, 1650, 1520, 1210, 1115, 660
34	H	L	Gly-OH	$C_7H_{13}N_3O_4S \cdot HCl$ 63- 68℃ decomp.	2	1.95(3H), 2.12(3H), 4.05(2H), 4.83(1H)	3800-2200, 1735, 1680, 1540, 1505, 1400, 1315, 1200, 655

Compounds 1 - 3, 5, 7 - 9, and 11 - 34 were isolated as respective hydrochlorides.

* ; measured by using DMSO-d_6 as the solvent and TMS as the internal standard.

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Preparation Examples

Preparation Example 1

(1) Compound 1 2 g
(2) lactose 196 g
(3) corn starch 50 g
(4) magnesium stearate 2 g

(1), (2) and 20 g of corn starch were mixed and granulated together with a paste made from 15 g of corn starch, to which 15 g of cornstarch and (4) were added. The mixture was compressed with a compress-tableting machine, to produce 2000 tablets of 3 mm in diameter containing 1 mg of (1) in each tablet.

Preparation Example 2

(1) Compound 2 4 g
(2) lactose 194 g
(3) corn starch 40 g
(4) magnesium stearate 2 g

(1), (2) and 15 g of corn starch were mixed and granulated together with a paste made from 15 g of corn starch, to which 10 g of corn starch and (4) were added. The mixture was compressed with a compress-tableting machine, to produce 2000 tablets of 5 mm in diameter containing 2 mg of (1) in each tablet.

Preparation Example 3

(1) Compound 1 100 mg
(2) Avicel (crystalline cellulose) 300 mg
(3) lactose 595 mg
(4) magnesium stearate 5 mg

(1), (2), (3) and (4) described above were mixed thoroughly, and compressed directly with a compress-tableting machine, to produce 100 sublingual tablets (3 mm in diameter) containing 1 mg of (1) in each tablet.

Experimental Example 1

In a 20 ml-tank (37°C, aerated with 95% O_2 + 5% CO_2, pH7.4), a specimen (pig left coronary descending artery (LAD), or rat aorta) was suspended. The specimen was allowed to contract by addition of $PGF_{2\alpha}$ (6 μM) for pig coronary artery or KCl (60 mM) or TEA (45 mM) + Ba (0.3 mM) for rat aorta, and then a test compound was added at a time or cumulatively; the relaxing effect of the compound on the constrictive tension was examined; the Compounds 1 and 2 showed a powerful relaxing effect.

Experiment Example 2

Relaxing effects on KC1 induced contraction in isolated rat aorta

Ring preparations of rat thoracic aorta were placed in 20mℓ organ baths containing Krebs-Hemseleit solution kept at 37°C, a pH of 7.4 and gassed with 95% CO_2 - 5% O_2. After steady state contraction induced by 60mM KC1, vasorelaxing effects of test compounds (10^{-6}, 10^{-7} mol/l) were examined. The vasorelaxing effects were expressed as % relaxation from the maximum contraction induced by 60mM KC1. The relaxing effects are shown in Table 3.

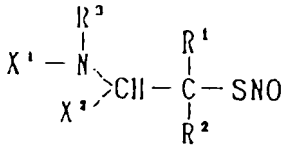
Table 3

Compound	10^{-7}M	Retension time/min	10^{-6}M	Retension time/min
2	18	24	62	> 30
3	19	17	50	> 30
5	16	25	47	> 30
7	11	> 30	64	> 30
11	12	20	37	> 30
13	19	> 30	85	> 30
14	11	12	74	> 30
17	20	17	66	> 30
19	19	20	58	> 30
24	26	> 30	75	> 30

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL, SE

1. A compound of the formula:



wherein R^1 and R^2 are independently a hydrogen atom or a hydrocarbon residue which may be substituted; R^3 is a hydrogen atom, an acyl group or a hydrocarbon residue which may be substituted; X^1 is a hydrogen atom, an acyl group, a lower alkoxy group or a hydrocarbon residue which may be substituted; X^2 is an acyl group or a carboxyl group which may be esterified or which may form an amide; with a proviso that when X^2 is a carboxyl group X^1 is not a hydrogen atom or acetyl group and that when both R^1 and R^2 are hydrogen atoms X^1 is not an acetyl group or γ-glutamyl group, or a salt thereof.

2. A compound according to claim 1, wherein R^1 and R^2 are independently a hydrocarbon residue which may be substituted, or R^1 and R^2 may be bound to each other to form a ring of the formula: $-(CH_2)_n-$ wherein n is an integer of 2 to 6.

3. A compound according to claim 1, wherein X^1 is an amino acid derived acyl.

4. A compound according to claim 1, wherein R^1 and R^2 are independently a hydrocarbon residue which may be substituted; R^3 is a hydrogen atom, an acyl group or a hydrocarbon residue which may be substituted; X^1 is an amino acid derived acyl; X^2 is an acyl group or a carboxyl group which may be esterified or which may form an amide.

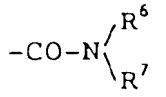
5. A compound according to claim 1, wherein the hydrocarbon residue represented by R^1, R^2, R^3 or X^1 is a chain saturated, chain unsaturated, cyclic saturated or cyclic unsaturated hydrocarbon residue, each of which may be substituted by one to three groups selected from the class consisting of halogen atom, nitro, nitrile, hydroxyl, carboxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl amino, mono- or di-aralkylamino, mono- or di-pyridylamino, C_{1-4} alkoxycarbonyl, cyclo C_{3-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkylcarbamoyl, and phenyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl C_{1-4} alkylcarbamoyl or phenylcarbamoyl group, in which each of said phenyl group may be substituted by 1 to 4 groups selected from the class consisting of C_{1-4} alkyl, halogen atom, hydroxyl, benzyloxy, amino, mono- or di-C_{1-4} alkylamino, niro and C_{1-4} alkoxycarbonyl.

6. A compound according to claim 1, wherein the acyl group represented by R^3, X^1 or X^2 is a carboxylic, carbamic, sulfonic or oxycarboxylic acyl group, each of which may be substituted by one to three groups selected from the class consisting of halogen atom, nitro, nitrile, hydroxyl, carboxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl amino, mono- or di-aralkylamino, mono- or di-pyridylcarbonylamino, C_{1-6} alkylcarbonyl, C_{1-4} alkoxycarbonyl, cyclo C_{3-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkylcarbamoyl, and phenyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl C_{1-4} alkylcarbamoyl or phenylcarbamoyl group, in which each of said phenyl may be substituted by 1 to 4 groups selected from the class consisting of C_{1-4} alkyl, halogen atom, hydroxyl, benzyloxy, amino, mono- or di-C_{1-4} alkylamino nitro and C_{1-4} alkoxycarbonyl.

7. A compound according to claim 1, wherein the lower alkoxy group is C_{1-6} alkoxy group.

8. A compound according to claim 1, wherein the carboxyl group which may be esterified is carboxyl or a group of the formula: -CO-OR^5
wherein R^5 is a hydrocarbon residue which may be substituted.

9. A compound according to claim 1, wherein the carboxyl group which may form an amide is carboxyl or a group of the formula:



wherein R^6 is a hydrogen atom or a hydrocarbon residue which may be substituted, and R^7 is a hydrogen atom or a lower alkyl group or R^6 and R^7 may form a cyclic amino group together with the adjacent nitrogen atom.

10. A compound according to Claim 1, wherein R^1 and R^2 are independently a chain saturated or cyclic unsaturated hydrocarbon residue, or R^1 and R^2 together with the adjacent carbon atom form cyclopentyl or cyclohexyl.

11. A compound according to claim 1, wherein R^1 and R^2 are independently C_{1-6}alkyl group.

12. A compound according to claim 1, wherein R^1 and R^2 are methyl.

13. A compound according to claim 1, wherein R^3 is a hydrogen atom or an acyl group.

14. A compound according to claim 13, wherein the acyl group is C_{1-6} alkyl carbonyl or C_{6-10} aryl carbonyl.

15. A compound according to claim 1, wherein R^3 is a hydrogen atom.

16. A compound according to claim 1, wherein X^1 is a hydrogen atom or an acyl group.

17. A compound according to claim 16, wherein the acyl group is an amino acid derived acyl group.

18. A compound according to claim 17, wherein the amino acid is glycine, alanine, glutamic acid, leucine, isoleucine, phenylalanine, aspartic acid, cysteine, sarcosine, glutamine, asparagine or proline.

19. A compound according to claim 17, wherein the amino acid is glycine, aspartic acid, asparagine, glutamic acid, glutamine or phenylalanine.

20. A compound according to claim 17, wherein the amino acid is glutamic acid or aspartic acid.

21. A compound according to claim 1, wherein X^2 is a carboxyl group which may be esterified.

22. A compound according to claim 1, wherein X^2 is a carboxyl or carbamic acyl group.

23. A compound according to claim 22, wherein the carbamic acyl group is carbonyl amino or a carboxyl group forming an amide with an amino acid.

24. A compound according to claim 23, wherein the amino acid is glycine, alanine, glutamic acid, leucine, isoleucine, phenylalanine, aspartic acid, cysteine, sarcosine, glutamine, asparagine or proline.

25. A compound according to claim 23, wherein the amino acid is glycine, aspartic acid, asparagine, phenylalanine, glutamic acid or glutamine.

26. A compound according to claim 1, wherein R^1 and R^2 are independently C_{1-6} alkyl, phenyl or naphthyl, or R^1 and R^2 form cyclopentyl or cyclohexyl together with the adjacent carbon atom; R^3 is a hydrogen atom or a C_{6-10} aromatic acyl group; X^1 is a hydrogen atom or an amino acid derived acyl group in which said amino acid is selected from the group consisting of glycine, aspartic acid, phenylalanine, asparagine, glutamic acid and glutamine; X^2 is a carboxyl group, carbonylamino or a carboxyl group forming an amide with an amino acid residue in which said amino acid is selected from the group consisting of glycine, aspartic acid, phenylalanine, asparagine, glutamic acid and glutamine.

27. A compound according to claim 1, wherein the salt is a pharmaceutically acceptable salt.

28. A compound according to claim 1, which is N-(N-L-γ-Glutamyl-D-penicillamyl)glycine.

29. A compound according to claim 1, which is N-(N-L-γ-Glutamyl-L-penicillamyl)-L-valine.

30. A compound according to claim 1, which is N-(N-L-γ-Glutamyl-L-penicillamyl)-L-phenylalanine.

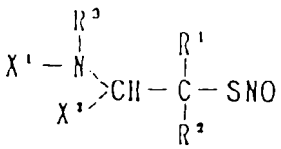
31. A compound according to claim 1, which is N-(N-L-γ-Glutamyl-L-penicillamyl)-L-glutamic acid.

32. A compound according to claim 1, which is N-(N-L-γ-Glutamyl-D-penicillamyl)diphenylmethylamine.

33. A pharmaceutical composition suitable for the therapy or prophylaxis of hypertension or angina pectoris which comprises (a) as the active ingredient, an effective amount of a compound according to claim 1 or a salt thereof and (b) a pharmaceutically acceptable carrier, excipient or diluent therefor.

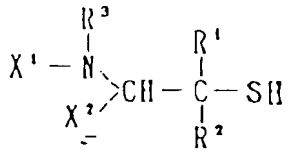
34. The use of a compound according to claim 1 or a salt thereof for the preparation of a medicine for the therapeutic treatment of a mammal.

35. A method for producing a compound of the formula (I) :



wherein R^1 and R^2 are independently a hydrogen atom or a hydrocarbon residue which may be substituted; R^3 is a hydrogen atom, an acyl group or a hydrocarbon residue which may be substituted; X^1 is a hydrogen atom, an acyl group, a lower alkoxy group or a hydrocarbon residue which may be substituted; X^2 is an acyl group or a carboxyl group which may be esterified or which may form an amide; with a proviso that when X^2 is a carboxyl group X^1 is not a hydrogen atom or acetyl group and that when both R^1 and R^2 are hydrogen atoms X^1 is not acetyl group or γ-glutamyl group, or a salt thereof, which comprises.

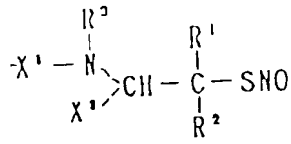
(a) subjecting a compound of the formula (II):



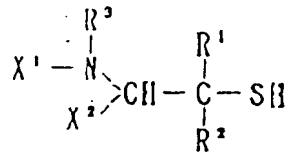
wherein R^1, R^2, R^3, X^1 and X^2 are the same as described above to the nitrosation reaction, and, if desired,
(b) converting a product obtained by the above process (a) into a salt thereof.

Claims for the following Contracting State : ES

1. A method for producing a compound of the formula (I):



wherein R^1 and R^2 are independently a hydrogen atom or a hydrocarbon residue which may be substituted; R^3 is a hydrogen atom, an acyl group or a hydrocarbon residue which may be substituted; X^1 is a hydrogen atom, an acyl group, a lower alkoxy group or a hydrocarbon residue which may be substituted; X^2 is an acyl group or a carboxyl group which may be esterified or which may form an amide; with a proviso that when X^2 is a carboxyl group X^1 is not a hydrogen atom or acetyl group and that when both R^1 and R^2 are hydrogen atoms X^1 is not acetyl group or -glutamyl group, or a salt thereof, which comprises.
(a) subjecting a compound of the formula (II):



wherein R^1, R^2, R^3, X^1 and X^2 are the same as described above to the nitrosation reaction, and, if desired,
(b) converting a product obtained by the above process (a) into a salt thereof.

2. A method according to claim 1, wherein R^1 and R^2 are independently a hydrocarbon residue which may be substituted, or R^1 and R^2 may be bound to each other to form a ring of the formula: $-(CH_2)_n-$ wherein n is an integer of 2 to 6.

3. A method according to claim 1, wherein X^1 is an amino acid derived acyl.

4. A method according to claim 1, wherein R^1 and R^2 are independently a hydrocarbon residue which may be substituted; R^3 is a hydrogen atom, an acyl group or a hydrocarbon residue which may be substituted; X^1 is an amino acid derived acyl; X^2 is an acyl group or a carboxyl group which may be esterified or which may form an amide.

5. A method according to claim 1, wherein the hydrocarbon residue represented by R^1, R^2, R^3 or X^1 is a chain saturated, chain unsaturated, cyclic saturated or cyclic unsaturated hydrocarbon residue, each of which may be substituted by one to three groups selected from the class consisting of halogen atom, nitro, nitrile, hydroxyl, carboxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl amino, mono-or di-aralkyla-

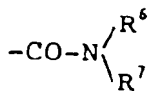
mino, mono- or di-pyridylamino, C_{1-4} alkoxycarbonyl, cyclo C_{3-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkylcarbamoyl, and phenyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl C_{1-4} alkylcarbamoyl or phenylcarbamoyl group, in which each of said phenyl group may be substituted by 1 to 4 groups selected from the class consisting of C_{1-4} alkyl, halogen atom, hydroxyl, benzyloxy, amino, mono- or di-C_{1-4} alkylamino, niro and C_{1-4} alkoxycarbonyl.

6. A method according to claim 1, wherein the acyl group represented by R^3, X^1 or X^2 is a carboxylic, carbamic, sulfonic or oxycarboxylic acyl group, each of which may be substituted by one to three groups selected from the class consisting of halogen atom, nitro, nitrile, hydroxyl, carboxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono- or di-C_{1-4} alkyl amino, mono- or di-aralkylamino, mono- or di-pyridylcarbonylamino, C_{1-6} alkylcarbonyl, C_{1-4} alkoxycarbonyl, cyclo C_{3-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkylcarbamoyl, and phenyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl C_{1-4} alkylcarbamoyl or phenylcarbamoyl group, in which each of said phenyl groups may be substituted by 1 to 4 groups selected from the class consisting of C_{1-4} alkyl, halogen atom, hydroxyl, benzyloxy, amino, mono- or di-C_{1-4} alkylamino nitro and C_{1-4} alkoxycarbonyl.

7. A method according to claim 1, wherein the lower alkoxy group is C_{1-6} alkoyl group.

8. A method according to claim 1, wherein the carboxyl group which may be esterified is carboxyl or a group of the formula: -CO-OR^5
wherein R^5 is a hydrocarbon residue which may be substituted.

9. A method according to claim 1, wherein the carboxyl group which may form an amide is carboxyl or a group of the formula:



wherein R^6 is a hydrogen atom or a hydrocarbon residue which may be substituted, and R^7 is a hydrogen atom or a lower alkyl group or R^6 and R^7 may form a cyclic amino group together with the adjacent nitrogen atom.

10. A method according to claim 1, wherein R^1 and R^2 are independently a chain saturated or cyclic unsaturated hydrocarbon residue, or R^1 and R^2 together with the adjacent carbon atom form cyclopentyl or cyclohexyl.

11. A method according to claim 1, wherein R^1 and R^2 are independently C_{1-6} alkyl group.

12. A method according to claim 1, wherein R^1 and R^2 are methyl.

13. A method according to claim 1, wherein R^3 is a hydrogen atom or an acyl group.

14. A method according to claim 13, wherein the acyl group is C_{1-6} alkyl carbonyl or C_{6-10} aryl carbonyl.

15. A method according to claim 1, wherein R^3 is a hydrogen atom.

16. A method according to claim 1, wherein X^1 is a hydrogen atom or an acyl group.

17. A method according to claim 16, wherein the acyl group is an amino acid derived acyl group.

18. A method according to claim 17, wherein the amino acid is glycine, alanine, glutamic acid, leucine, isoleucine, phenylalanine, aspartic acid, cysteine, sarcosine, glutamine, asparagine or proline.

19. A method according to claim 17, wherein the amino acid is glycine, aspartic acid, asparagine, glutamic acid, glutamine or phenylalanine.

20. A method according to claim 17, wherein the amino acid is glutamic acid or aspartic acid.

21. A method according to claim 1, wherein X^2 is a carboxyl group which may be esterified.

22. A method according to claim 1, wherein X^2 is a carboxyl or carbamic acyl group.

23. A method according to claim 22, wherein the carbamic acyl group is carbonyl amino or a carboxyl group forming an amide with an amino acid.

24. A method according to claim 23, wherein the amino acid is glycine, alanine, glutamic acid, leucine, isoleucine, phenylalanine, aspartic acid, cysteine, sarcosine, glutamine, asparagine or proline.

25. A method according to claim 23, wherein the amino acid is glycine, aspartic acid, asparagine, pheylalanine, glutamic acid or glutamine.

26. A method according to claim 1, wherein R^1 and R^2 are independently C_{1-6} alkyl, phenyl or naphthyl, or R^1 and R^2 form cyclopentyl or cyclohexyl together with the adjacent carbon atom; R^3 is a hydrogen atom or a C_{6-10} aromatic acyl group; X^1 is a hydrogen atom or an amino acid derived acyl group in which said amino acid is selected from the group consisting of glycine, aspartic acid, phenylalanine, asparagine, glutamic acid and glutamine; X^2 is a carboxyl group, carbonylamino or a carboxyl group forming an amide with an amino acid residue in which said amino acid is selected from the group consisting of glycine, aspartic acid, phenylalanine, asparagine, glutamic acid and glutamine.

27. A method according to claim 1, wherein the salt is a pharmaceutically acceptable salt.

28. A method according to claim 1, wherein said compound (I) is N-(N-L-γ-Glutamyl-D-penicillamyl)glycine.

29. A method according to claim 1, wherein said compound (I) is N-(N-L-γ-Glutamyl-L-penicillamyl)-L-valine.

30. A method according to claim 1, wherein said compound (I) is N-(N-L-γ-Glutamyl-L-penicillamyl)-L-phenylalanine.

31. A method of a compound according to claim 1, wherein said compound (I) is N-(N-L-γ-Glutamyl-L-penicillamyl)-L-glutamic acid.

32. A method according to claim 1, wherein siad compound (I) is N-(N-L-γ-Glutamyl-D-penicillamyl)diphenylmethylamine.

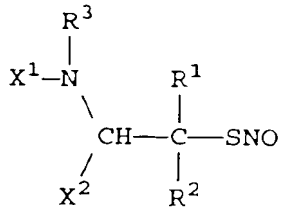
33. A pharmaceutical composition for use in preparation of a medicine suitable for the therapy or prophylaxis of hypertension or angina pectoris which comprises (a) as the active ingredient, an effective amount of a compound as defined in claim 1 or a salt thereof and (b) a pharmaceutically acceptable carrier, excipient or diluent therefor.

34. The use of a compound as defined in claim 1 or a salt thereof for the preparation of a medicine for the therapeutic treatment of a mammal.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL, SE

1. Verbindung der Formel



worin

R^1 und R^2 unabhängig ein Wasserstoff-Atom oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, sind;

R^3 ein Wasserstoff-Atom, eine Acyl-Gruppe, oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, ist;

X^1 ein Wasserstoff-Atom, eine Acyl-Gruppe, eine niedere Alkoxy-Gruppe oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, ist;

X^2 eine Acyl-Gruppe oder eine Carboxyl-Gruppe, die verestert sein oder ein Amid bilden kann, ist;

mit der Maßgabe,

daß dann, wenn X^2 eine Carboxyl-Gruppe ist, X^1 nicht ein Wasserstoff-Atom oder eine Acetyl-Gruppe ist und

daß dann, wenn R^1 und R^2 beide Wasserstoff-Atome sind, X^1 nicht eine Acetyl-Gruppe oder eine γ-Glutamyl-Gruppe ist, oder ein Salz derselben.

2. Verbindung nach Anspruch 1, worin R^1 und R^2 unabhängig ein Kohlenwasserstoff-Rest, der substituiert sein kann, sind oder R^1 und R^2 aneinander gebunden sein können und dann einen Ring der Formel $-(CH_2)_n-$ bilden, worin n eine ganze Zahl von 2 bis 6 ist.

3. Verbindung nach Anspruch 1, worin X^1 ein von einer Aminosäure abgeleitetes Acyl ist.

4. Verbindung nach Anspruch 1, worin

R^1 und R^2 unabhängig ein Kohlenwasserstoff-Rest, der substituiert sein kann, sind;

R^3 ein Wasserstoff-Atom, eine Acyl-Gruppe, oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, ist;

X^1 ein von einer Aminosäure abgeleitetes Acyl ist;

X^2 eine Acyl-Gruppe oder eine Carboxyl-Gruppe, die verestert sein oder ein Amid bilden kann, ist.

5. Verbindung nach Anspruch 1, worin der Kohlenwasserstoff-Rest, der durch R^1, R^2, R^3 oder X^1 dargestellt wird, ein kettengesättigter, kettenungesättigter, cyclisch-gesättigter oder cyclisch-ungesättigter Kohlenwasserstoff-Rest ist, der jeweils durch eine bis drei Gruppen substituiert sein kann, die aus der aus einem Halogen-Atom, Nitro, Nitril, Hydroxy, Carboxyl, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Amino, Mono- oder Di-C_{1-4}-alkylamino, Mono- oder Di- aralkylamino, Mono- oder Dipyridylamino, C_{1-4}-Alkoxycarbonyl, Cyclo-C_{3-6}-alkylcarbonyl, Carbamoyl, Mono- oder Di-C_{1-4}-alkylcarbamoyl und Phenyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C_{1-4}-alkylcarbamoyl oder der Phenylcarbamoyl-Gruppe bestehenden Klasse ausgewählt sein können, wobei jede der genannten Phenyl-Gruppen durch 1 bis 4 Gruppen substituiert sein kann, die aus der aus C_{1-4}-Alkyl, einem Halogen-Atom, Hydroxyl, Benzyloxy, Amino, Mono- oder Di-C_{1-4}-alkylamino, Nitro und C_{1-4}-Alkoxycarbonyl bestehenden Klasse ausgewählt sein können.

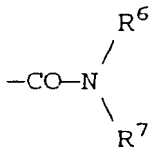
6. Verbindung nach Anspruch 1, worin die Acyl-Gruppe, die durch R^3, X^1 oder X^2 dargestellt wird, eine Carbonsäure-, Carbaminsäure-, Sulfonsäure- oder Oxycarbonsäure-Acyl-Gruppe ist, die jeweils durch eine bis drei Gruppen substituiert sein kann, die aus der aus einem Halogen-Atom, Nitro, Nitril, Hydroxy, Carboxyl, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Amino, Mono- oder Di-C_{1-4}-alkylamino, Mono- oder Diaralkylamino, Mono- oder Dipyridylcarbonylamino, C_{1-6}-Alkylcarbonyl, C_{1-4}-Alkoxycarbonyl, Cyclo-C_{3-6}-alkylcarbonyl, Carbamoyl, Mono- oder Di-C_{1-4}-alkylcarbamoyl und Phenyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C_{1-4}-alkylcarbamoyl oder der Phenylcarbamoyl-Gruppe bestehenden Klasse ausgewählt sein können, wobei jede der genannten Phenyl-Gruppen durch 1 bis 4 Gruppen substituiert sein kann, die aus

der aus C_{1-4}-Alkyl, einem Halogen-Atom, Hydroxyl, Benzyloxy, Amino, Mono- oder Di-C_{1-4}-alkylamino, Nitro und C_{1-4}-Alkoxycarbonyl bestehenden Klasse ausgewählt sein können.

7. Verbindung nach Anspruch 1, worin die niedere Alkoxy-Gruppe eine C_{1-6}-Alkoxy-Gruppe ist.

8. Verbindung nach Anspruch 1, worin die Carboxyl-Gruppe, die verestert sein kann, Carboxyl oder eine Gruppe der Formel -CO-OR^5 ist, worin R^5 ein Kohlenwasserstoff-Rest ist, der substituiert sein kann.

9. Verbindung nach Anspruch 1, worin die Carboxyl-Gruppe, die ein Amid bilden kann, Carboxyl oder eine Gruppe der Formel



ist, worin

R^6	ein Wasserstoff-Atom oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, ist und
R^7	ein Wasserstoff-Atom oder eine niedere Alkyl-Gruppe ist oder
R^6 und R^7	zusammen mit dem benachbarten Stickstoff-Atom eine cyclische Amino-Gruppe bilden können.

10. Verbindung nach Anspruch 1, worin R^1 und R^2 unabhängig ein kettengesättigter oder ein cyclisch-ungesättigter Kohlenwasserstoff-Rest sind oder R^{1}und R^2 zusammen mit dem benachbarten Kohlenstoff-Atom Cyclopentyl oder Cyclohexyl bilden.

11. Verbindung nach Anspruch 1, worin R^1 und R^2 unabhängig eine C_{1-6}-Alkyl-Gruppe sind.

12. Verbindung nach Anspruch 1, worin R^1 und R^2 Methyl sind.

13. Verbindung nach Anspruch 1, worin R^3 ein Wasserstoff-Atom oder eine Acyl-Gruppe ist.

14. Verbindung nach Anspruch 13, worin die Acyl-Gruppe C_{1-6}-Alkylcarbonyl- oder C_{6-10}Arylcarbonyl ist.

15. Verbindung nach Anspruch 1, worin R^3 ein Wasserstoff-Atom ist.

16. Verbindung nach Anspruch 1, worin X^1 ein Wasserstoff-Atom oder eine Acyl-Gruppe ist.

17. Verbindung nach Anspruch 16, worin die Acyl-Gruppe eine von einer Aminosäure abgeleitete Acyl-Gruppe ist.

18. Verbindung nach Anspruch 17, worin die Aminosäure Glycin, Alanin, Glutaminsäure, Leucin, Isoleucin, Phenylalanin, Asparaginsäure, Cystein, Sarcosin, Glutamin, Asparagin oder Prolin ist.

19. Verbindung nach Anspruch 17, worin die Aminosäure Glycin, Asparaginsäure, Asparagin, Glutaminsäure, Glutamin oder Phenylalanin ist.

20. Verbindung nach Anspruch 17, worin die Aminosäure Glutaminsäure oder Asparaginsäure ist.

21. Verbindung nach Anspruch 1, worin X^2 eine Carboxyl-Gruppe ist, die verestert sein kann.

22. Verbindung nach Anspruch 1, worin X^2 eine Carboxyl- oder eine Carbaminsäure-Acyl-Gruppe ist.

23. Verbindung nach Anspruch 22, worin die Carbaminsäure-Acyl-Gruppe Carbonylamino oder eine mit einer Aminosäure ein Amid bildende Carboxyl-Gruppe ist.

24. Verbindung nach Anspruch 23, worin die Aminosäure Glycin, Alanin, Glutaminsäure, Leucin, Isoleucin, Phenylalanin, Asparaginsäure, Cystein, Sarcosin, Glutamin, Asparagin oder Prolin ist.

25. Verbindung nach Anspruch 23, worin die Aminosäure Glycin, Asparaginsäure, Asparagin, Phenylalanin, Glutaminsäure oder Glutamin ist.

26. Verbindung nach Anspruch 1, worin

R^1 und R^2	unabhängig C_{1-6}-Alkyl, Phenyl oder Naphthyl sind oder R^1 und R^2 zusammen mit dem benachbarten Kohlenstoff-Atom Cyclopentyl oder Cyclohexyl bilden;
R^3	ein Wasserstoff-Atom oder eine aromatische C_{6-10}-Acyl-Gruppe ist;
X^1	ein Wasserstoff-Atom oder eine von einer Aminosäure abgeleitete Acyl-Gruppe ist, wobei die Aminosäure aus der aus Glycin, Asparaginsäure, Phenylalanin, Asparagin, Glutaminsäure und Glutamin bestehenden Gruppe ausgewählt ist;
X^2	eine Carboxyl-Gruppe, Carbonylamino oder eine mit einem Aminosäure-Rest ein Amid bildende Carboxyl-Gruppe ist, wobei die Aminosäure aus der aus Glycin, Asparaginsäure, Phenylalanin, Asparagin, Glutaminsäure und Glutamin bestehenden Gruppe ausgewählt ist.

27. Verbindung nach Anspruch 1, worin das Salz ein pharmazeutisch unbedenkliches Salz ist.

28. Verbindung nach Anspruch 1, die N-(N-L-γ-Glutamyl-D-penicillamyl)glycin ist.

29. Verbindung nach Anspruch 1, die N-(N-L-γ-Glutamyl-L-penicillamyl)-L-valin ist.

30. Verbindung nach Anspruch 1, die N-(N-L-γ-Glutamyl-L-penicillamyl)-L-phenylalanin ist.

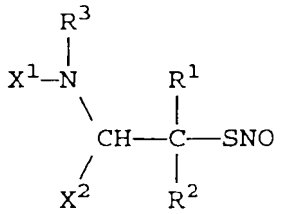
31. Verbindung nach Anspruch 1, die N-(N-L-γ-Glutamyl-L-penicillamyl)-L-glutaminsäure ist.

32. Verbindung nach Anspruch 1, die N-(N-L-γ-Glutamyl-D-penicillamyl)diphenylmethylamin ist.

33. Pharmazeutische Zusammensetzung, die für die Therapie oder Prophylaxe von Bluthochdruck oder Angina pectoris geeignet ist, umfassend
(a) als Wirkstoff eine wirksame Menge einer Verbindung nach Anspruch 1 oder eines Salzes derselben und
(b) ein pharmazeutisch unbedenkliches Trägermaterial, Streckmittel oder Verdünnungsmittel für diese.

34. Verwendung einer Verbindung nach Anspruch 1 oder eines Salzes derselben zu Herstellung eines Medikaments zur therapeutischen Behandlung eines Säugers.

35. Verfahren zur Herstellung einer Verbindung der Formel (I)

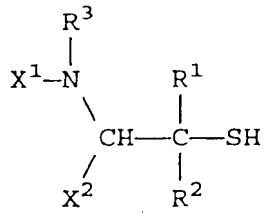


worin

R^1 und R^2	unabhängig ein Wasserstoff-Atom oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, sind;
R^3	ein Wasserstoff-Atom, eine Acyl-Gruppe, oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, ist;
X^1	ein Wasserstoff-Atom, eine Acyl-Gruppe, eine niedere Alkoxy-Gruppe oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, ist;
X^2	eine Acyl-Gruppe oder eine Carboxyl-Gruppe, die verestert sein oder ein Amid bilden kann, ist;

mit der Maßgabe,
daß dann, wenn X^2 eine Carboxyl-Gruppe ist, X^1 nicht ein Wasserstoff-Atom oder eine Acetyl-Gruppe ist und

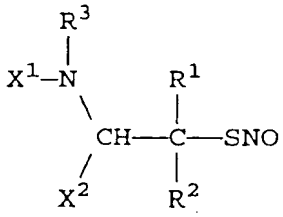
daß dann, wenn R^1 und R^2 beide Wasserstoff-Atome sind, X^1 nicht eine Acetyl-Gruppe oder eine γ-Glutamyl-Gruppe ist, oder eines Salzes derselben,
umfassend
(a) die Durchführung einer Nitrosierungs-Reaktion mit einer Verbindung der Formel (II)



worin
R^1, R^2, R^3, X^1 und X^2 die gleichen sind, wie sie oben beschrieben sind, und gewünschtenfalls
(b) die Überführung des durch das obige Verfahren (a) erhaltenen Produkts in ein Salz desselben.

Patentansprüche für folgenden Vertragsstaat : ES

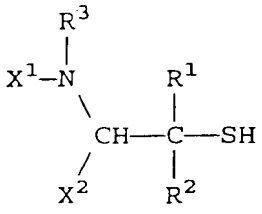
1. Verfahren zur Herstellung einer Verbindung der Formel (I)



worin

R^1 und R^2	unabhängig ein Wasserstoff-Atom oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, sind;
R^3	ein Wasserstoff-Atom, eine Acyl-Gruppe, oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, ist;
X^1	ein Wasserstoff-Atom, eine Acyl-Gruppe, eine niedere Alkoxy-Gruppe oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, ist;
X^2	eine Acyl-Gruppe oder eine Carboxyl-Gruppe, die verestert sein oder ein Amid bilden kann, ist;

mit der Maßgabe,
daß dann, wenn X^2 eine Carboxyl-Gruppe ist, X^1 nicht ein Wasserstoff-Atom oder eine Acetyl-Gruppe ist und
daß dann, wenn R^1 und R^2 beide Wasserstoff-Atome sind, X^1 nicht eine Acetyl-Gruppe oder eine γ-Glutamyl-Gruppe ist, oder eines Salzes derselben,
umfassend
(a) die Durchführung einer Nitrosierungs-Reaktion mit einer Verbindung der Formel (II)



worin
R^1, R^2, R^3, X^1 und X^2 die gleichen sind, wie sie oben beschrieben sind, und gewünschtenfalls
(b) die Überführung des durch das obige Verfahren (a) erhaltenen Produkts in ein Salz desselben.

2. Verfahren nach Anspruch 1, worin R^1 und R^2 unabhängig ein Kohlenwasserstoff-Rest, der substituiert sein kann, sind oder R^1 und R^2 aneinander gebunden sein können und dann einen Ring der Formel $-(CH_2)_n-$ bilden, worin n eine ganze Zahl von 2 bis 6 ist.

3. Verfahren nach Anspruch 1, worin X^1 ein von einer Aminosäure abgeleitetes Acyl ist.

4. Verfahren nach Anspruch 1, worin

R^1 und R^2	unabhängig ein Kohlenwasserstoff-Rest, der substituiert sein kann, sind;
R^3	ein Wasserstoff-Atom, eine Acyl-Gruppe, oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, ist;
X^1	ein von einer Aminosäure abgeleitetes Acyl ist;
X^2	eine Acyl-Gruppe oder eine Carboxyl-Gruppe, die verestert sein oder ein Amid bilden kann, ist.

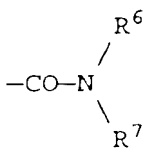
5. Verfahren nach Anspruch 1, worin der Kohlenwasserstoff-Rest, der durch R^1, R^2, R^3 oder X^1 dargestellt wird, ein kettengesättigter, kettenungesättigter, cyclisch-gesättigter oder cyclisch-ungesättigter Kohlenwasserstoff-Rest ist, der jeweils durch eine bis drei Gruppen substituiert sein kann, die aus der aus einem Halogen-Atom, Nitro, Nitril, Hydroxy, Carboxyl, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Amino, Mono- oder Di-C_{1-4}-alkylamino, Mono- oder Di-aralkylamino, Mono- oder Dipyridylamino, C_{1-4}-Alkoxycarbonyl, Cyclo-C_{3-6}-alkylcarbonyl, Carbamoyl, Mono- oder Di-C_{1-4}-alkylcarbamoyl und Phenyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C_{1-4}-alkylcarbamoyl oder der Phenylcarbamoyl-Gruppe bestehenden Klasse ausgewählt sein können, wobei jede der genannten Phenyl-Gruppen durch 1 bis 4 Gruppen substituiert sein kann, die aus der aus C_{1-4}-Alkyl, einem Halogen-Atom, Hydroxyl, Benzyloxy, Amino, Mono- oder Di-C_{1-4}-alkylamino, Nitro und C_{1-4}-Alkoxycarbonyl bestehenden Klasse ausgewählt sein können.

6. Verfahren nach Anspruch 1, worin die Acyl-Gruppe, die durch R^3, X^1 oder X^2 dargestellt wird, eine Carbonsäure-, Carbaminsäure-, Sulfonsäure- oder Oxycarbonsäure-Acyl-Gruppe ist, die jeweils durch eine bis drei Gruppen substituiert sein kann, die aus der aus einem Halogen-Atom, Nitro, Nitril, Hydroxy, Carboxyl, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Amino, Mono- oder Di-C_{1-4}-alkylamino, Mono- oder Diaralkylamino, Mono- oder Dipyridylcarbonylamino, C_{1-6}-Alkylcarbonyl, C_{1-4}-Alkoxycarbonyl, Cyclo-C_{3-6}-alkylcarbonyl, Carbamoyl, Mono- oder Di-C_{1-4}-alkylcarbamoyl und Phenyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C_{1-4}-alkylcarbamoyl oder der Phenylcarbamoyl-Gruppe bestehenden Klasse ausgewählt sein können, wobei jede der genannten Phenyl-Gruppen durch 1 bis 4 Gruppen substituiert sein kann, die aus der aus C_{1-4}-Alkyl, einem Halogen-Atom, Hydroxyl, Benzyloxy, Amino, Mono- oder Di-C_{1-4}-alkylamino, Nitro und C_{1-4}-Alkoxycarbonyl bestehenden Klasse ausgewählt sein können.

7. Verfahren nach Anspruch 1, worin die niedere Alkoxy-Gruppe eine C_{1-6}-Alkoxy-Gruppe ist.

8. Verfahren nach Anspruch 1, worin die Carboxyl-Gruppe, die verestert sein kann, Carboxyl oder eine Gruppe der Formel $-CO-OR^5$ ist, worin R^5 ein Kohlenwasserstoff-Rest ist, der substituiert sein kann.

9. Verfahren nach Anspruch 1, worin die Carboxyl-Gruppe, die ein Amid bilden kann, Carboxyl oder eine Gruppe der Formel



ist, worin

R^6	ein Wasserstoff-Atom oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, ist und
R^7	ein Wasserstoff-Atom oder eine niedere Alkyl-Gruppe ist oder

R^6 und R^7 zusammen mit dem benachbarten Stickstoff-Atom eine cyclische Amino-Gruppe bilden können.

10. Verfahren nach Anspruch 1, worin R^1 und R^2 unabhängig ein kettengesättigter oder ein cyclisch-ungesättigter Kohlenwasserstoff-Rest sind oder R^1und R^2 zusammen mit dem benachbarten Kohlenstoff-Atom Cyclopentyl oder Cyclohexyl bilden.

11. Verfahren nach Anspruch 1, worin R^1 und R^2 unabhängig eine C_{1-6}-Alkyl-Gruppe sind.

12. Verfahren nach Anspruch 1, worin R^1 und R^2 Methyl sind.

13. Verfahren nach Anspruch 1, worin R^3 ein Wasserstoff-Atom oder eine Acyl-Gruppe'ist.

14. Verfahren nach Anspruch 13, worin die Acyl-Gruppe C_{1-6}-Alkylcarbonyl- oder C_{6-10}Arylcarbonyl ist.

15. Verfahren nach Anspruch 1, worin R^3 ein Wasserstoff-Atom ist.

16. Verfahren nach Anspruch 1, worin X^1 ein Wasserstoff-Atom oder eine Acyl-Gruppe ist.

17. Verfahren nach Anspruch 16, worin die Acyl-Gruppe eine von einer Aminosäure abgeleitete Acyl-Gruppe ist.

18. Verfahren nach Anspruch 17, worin die Aminosäure Glycin, Alanin, Glutaminsäure, Leucin, Isoleucin, Phenylalanin, Asparaginsäure, Cystein, Sarcosin, Glutamin, Asparagin oder Prolin ist.

19. Verfahren nach Anspruch 17, worin die Aminosäure Glycin, Asparaginsäure, Asparagin, Glutaminsäure, Glutamin oder Phenylalanin ist.

20. Verfahren nach Anspruch 17, worin die Aminosäure Glutaminsäure oder Asparaginsäure ist.

21. Verfahren nach Anspruch 1, worin X^2 eine Carboxyl-Gruppe ist, die verestert sein kann.

22. Verfahren nach Anspruch 1, worin X^2 eine Carboxyl- oder eine Carbaminsäure-Acyl-Gruppe ist.

23. Verfahren nach Anspruch 22, worin die Carbaminsäure-Acyl-Gruppe Carbonylamino oder eine mit einer Aminosäure ein Amid bildende Carboxyl-Gruppe ist.

24. Verfahren nach Anspruch 23, worin die Aminosäure Glycin, Alanin, Glutaminsäure, Leucin, Isoleucin, Phenylalanin, Asparaginsäure, Cystein, Sarcosin, Glutamin, Asparagin oder Prolin ist.

25. Verfahren nach Anspruch 23, worin die Aminosäure Glycin, Asparaginsäure, Asparagin, Phenylalanin, Glutaminsäure oder Glutamin ist.

26. Verfahren nach Anspruch 1, worin

R^1 und R^2 unabhängig C_{1-6}-Alkyl, Phenyl oder Naphthyl sind oder R^1 und R^2 zusammen mit dem benachbarten Kohlenstoff-Atom Cyclopentyl oder Cyclohexyl bilden;

R^3 ein Wasserstoff-Atom oder eine aromatische C_{6-10}-Acyl-Gruppe ist;

X^1 ein Wasserstoff-Atom oder eine von einer Aminosäure abgeleitete Acyl-Gruppe ist, wobei die Aminosäure aus der aus Glycin, Asparaginsäure, Phenylalanin, Asparagin, Glutaminsäure und Glutamin bestehenden Gruppe ausgewählt ist;

X^2 eine Carboxyl-Gruppe, Carbonylamino oder eine mit einem Aminosäure-Rest ein Amid bildende Carboxyl-Gruppe ist, wobei die Aminosäure aus der aus Glycin, Asparaginsäure, Phenylalanin, Asparagin, Glutaminsäure und Glutamin bestehenden Gruppe ausgewählt ist.

27. Verfahren nach Anspruch 1, worin das Salz ein pharmazeutisch unbedenkliches Salz ist.

28. Verfahren nach Anspruch 1, die N-(N-L-γ-Glutamyl-D-penicillamyl)glycin ist.

29. Verfahren nach Anspruch 1, die N-(N-L-γ-Glutamyl-L-penicillamyl)-L-valin ist.

30. Verfahren nach Anspruch 1, die N-(N-L-γ-Glutamyl-L-penicillamyl)-L-phenylalanin ist.

31. Verfahren nach Anspruch 1, die N-(N-L-γ-Glutamyl-L-penicillamyl)-L-glutaminsäure ist.

32. Verfahren nach Anspruch 1, die N-(N-L-γ-Glutamyl-D-penicillamyl)diphenylmethylamin ist.

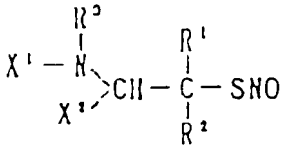
33. Pharmazeutische Zusammensetzung, die für die Therapie oder Prophylaxe von Bluthochdruck oder Angina pectoris geeignet ist, umfassend
(a) als Wirkstoff eine wirksame Menge einer Verbindung, wie sie in Anspruch 1 definiert ist, oder eines Salzes derselben und
(b) ein pharmazeutisch unbedenkliches Trägermaterial, Streckmittel oder Verdünnungsmittel für diese.

34. Verwendung einer Verbindung, wie sie in Anspruch 1 definiert ist, oder eines Salzes derselben zu Herstellung eines Medikaments zur therapeutischen Behandlung eines Säugers.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL, SE

1. Composé de formule:



dans laquelle R^1 et R^2 sont, indépendamment l'un de l'autre, un atome d'hydrogène ou un radical hydrocarboné qui peut être substitué; R^3 est un atome d'hydrogène, un groupe acyle ou un radical hydrocarboné qui peut être substitué; X^1 est un atome d'hydrogène, un groupe acyle, un groupe alcoxy inférieur ou un radical hydrocarboné qui peut être substitué; X^2 est un groupe acyle ou un groupe carboxylique qui peut être estérifié ou qui peut former un amide; avec la condition que X^1 n'est pas un atome d'hydrogène ou le groupe acétyle lorsque X^2 est un groupe carboxylique et que X^1 n'est pas un groupe acétyle ou un groupe γ-glutamyle lorsque R^1 et R^2 sont tous deux des atomes d'hydrogène, ou un sel de celui-ci.

2. Composé selon la revendication 1, dans lequel R^1 et R^2 sont, indépendamment l'un de l'autre, un radical hydrocarboné qui peut être substitué ou R^1 et R^2 peuvent être liés l'un à l'autre pour former un cycle de formule: $-(CH_2)_n-$ dans laquelle n est un nombre entier de 2 à 6.

3. Composé selon la revendication 1, dans lequel X^1 est un acyle dérivé d'un acide aminé.

4. Composé selon la revendication 1, dans lequel R^1 et R^2 sont, indépendamment l'un de l'autre, un radical hydrocarboné qui peut être substitué; R^3 est un atome d'hydrogène, un groupe acyle ou un radical hydrocarboné qui peut être substitué; X^1 est un acyle dérivé d'un acide aminé; X^2 est un groupe acyle ou un groupe carboxylique qui peut être estérifié ou qui peut former un amide.

5. Composé selon la revendication 1, dans lequel le radical hydrocarboné représenté par R^1, R^2, R^3 ou X^1 est un radical hydrocarboné à chaîne saturée, à chaîne insaturée, un radical hydrocarboné cyclique saturé ou cyclique insaturé, dont chacun peut être substitué par un à trois groupes choisis dans le groupe consistant en un atome d'halogène, un groupe nitro, nitrile, hydroxyle, carboxylique, alcoxy en C_{1-4}, alcoylthio en C_{1-4}, amino, mono ou di(alcoyle en C_{1-4})amino, mono ou di-aralcolyamino, mono ou di-pyridylamino, alcoxy en C_{1-4}-carbonyle, cycloalcoyle en C_{3-6}-carbonyle, carbamoyle, mono ou di(alcoyle en C_{1-4})carbamoyle et un groupe phényle, phénoxy, benzoyle, phénoxycarbonyle, phénylalcoyle en C_{1-4}-carbamoyle ou phénylcarbamoyle, dans lesquels chacun desdits groupes phényle peut être substitué par 1 à 4 groupes choisis dans le groupe consistant en un alcoyle en C_{1-4}, un atome d'halogène, un groupe hydroxyle, ben-

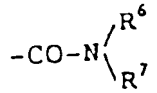
zyloxy, amino, mono ou di(alcoyle en C_{1-4})amino, nitro et alcoxy en C_{1-4}-carbonyle.

6. Composé selon la revendication 1, dans lequel le groupe acyle représenté par R^3, X^1 ou X^2 est un groupe acyle carboxylique, carbamique, sulfonique ou oxycarboxylique dont chacun peut être substitué par 1 à 3 groupes choisis dans le groupe consistant en un atome d'halogène, un groupe nitro, nitrile, hydroxyle, carboxylique, alcoxy en C_{1-4}, alcoylthio en C_{1-4}, amino, mono ou di(alcoyle en C_{1-4})amino, mono ou di-aralcoylamino, mono ou di-pyridylcarbonylamino, alcoyle en C_{1-6}-carbonyle, alcoxy en C_{1-4}-carbonyle, cycloalcoyle en C_{3-6}-carbonyle, carbamoyle, mono ou di(alcoyle en C_{1-4})-carbamoyle et un groupe phényle, phénoxy, benzoyle, phénoxycarbonyle, phényl-alcoyle en C_{1-4}-carbamoyle ou phénylcarbamoyle dans lesquels chacun desdits groupes phényle peut être substitué par 1 à 4 groupes choisis dans le groupe consistant en un alcoyle en C_{1-4}, un atome d'halogène, un groupe hydroxyle, benzyloxy, amino, mono ou di(alcoyle en C_{1-4})amino, nitro et alcoxy en C_{1-4}-carbonyle.

7. Composé selon la revendication 1, dans lequel le groupe alcoxy inférieur est un groupe alcoxy en C_{1-6}.

8. Composé selon la revendication 1, dans lequel le groupe carboxylique qui peut être estérifié est un carboxyle ou un groupe de formule: -CO-OR^5, dans laquelle R^5 est un radical hydrocarboné qui peut être substitué.

9. Composé selon la revendication 1, dans lequel le groupe carboxylique qui peut former un amide est un carboxyle ou un groupe de formule:



dans laquelle R^6 est un atome d'hydrogène ou un radical hydrocarboné qui peut être substitué et R^7 est un atome d'hydrogène ou un groupe alcoyle inférieur ou R^6 et R^7 forment ensemble avec l'atome d'azote adjacent un groupe amino cyclique.

10. Composé selon la revendication 1, dans lequel R^1 et R^2 sont, indépendamment l'un de l'autre, un radical hydrocarboné à chaîne saturée ou cyclique insaturée ou R^1 et R^2 forment ensemble avec l'atome de carbone adjacent un groupe cyclopentyle ou cyclohexyle.

11. Composé selon la revendication 1, dans lequel R^1 et R^2 sont, indépendamment l'un de l'autre, un groupe alcoyle en C_{1-6}.

12. Composé selon la revendication 1, dans lequel R^1 et R^2 sont un méthyle.

13. Composé selon la revendication 1, dans lequel R^3 est un atome d'hydrogène ou un groupe acyle.

14. Composé selon la revendication 13, dans lequel le groupe acyle est un alcoyle en C_{1-6}-carbonyle ou un aryle en C_{6-10}-carbonyle.

15. Composé selon la revendication 1, dans lequel R^3 est un atome d'hydrogène.

16. Composé selon la revendication 1, dans lequel X^1 est un atome d'hydrogène ou un groupe acyle.

17. Composé selon la revendication 16, dans lequel le groupe acyle est un groupe acyle dérivé d'un acide aminé.

18. Composé selon la revendication 17, dans lequel l'acide aminé est la glycine, l'alanine, l'acide glutamique, la leucine, l'isoleucine, la phénylalanine, l'acide aspartique, la cystéine, la sarcosine, la glutamine, l'asparagine ou la proline.

19. Composé selon la revendication 17, dans lequel l'acide aminé est la glycine, l'acide aspartique, l'asparagine, l'acide glutamique, la glutamine ou la phénylalanine.

20. Composé selon la revendication 17, dans lequel l'acide aminé est l'acide glutamique ou l'acide aspartique.

21. Composé selon la revendication 1, dans lequel X^2 est un groupe carboxylique qui peut être estérifié.

22. Composé selon la revendication 1, dans lequel X^2 est un groupe acyle carboxylique ou carbamique.

23. Composé selon la revendication 22, dans lequel le groupe acyle carbamique est un groupe aminocarbonyle ou un groupe carboxylique formant un amide avec un acide aminé.

24. Composé selon la revendication 23, dans lequel l'acide aminé est la glycine, l'alanine, l'acide glutamique, la leucine, l'isoleucine, la phénylalanine, l'acide aspartique, la cystéine, la sarcosine, la glutamine, l'asparagine ou la proline.

25. Composé selon la revendication 23, dans lequel l'acide aminé est la glycine, l'acide aspartique, l'asparagine, la phénylalanine, l'acide glutamique ou la glutamine.

26. Composé selon la revendication 1, dans lequel R^1 et R^2 sont, indépendamment l'un de l'autre, un groupe alcoyle en C_{1-6}, phényle ou naphtyle ou R^1 et R^2 forment ensemble avec l'atome de carbone adjacent un groupe cyclopentyle ou cyclohexyle; R^3 est un atome d'hydrogène ou un groupe acyle aromatique en C_{6-10}; X^1 est un atome d'hydrogène ou un groupe acyle dérivé d'un acide aminé dans lequel ledit acide aminé est choisi dans le groupe consistant en la glycine, l'acide aspartique, la phénylalanine, l'asparagine, l'acide glutamique et la glutamine; X^2 est un groupe carboxylique, aminocarbonyle ou un groupe carboxylique formant un amide avec un radical d'acide aminé dans lequel ledit acide aminé est choisi dans le groupe consistant en la glycine, l'acide aspartique, la phénylalanine, l'asparagine, l'acide glutamique et la glutamine.

27. Composé selon la revendication 1, dans lequel le sel est un sel pharmaceutiquement acceptable.

28. Composé selon la revendication 1, qui est la N-(N-L-γ-glutamyl-D-pénicillamyl)glycine.

29. Composé selon la revendication 1, qui est la N-(N-L-γ-glutamyl-L-pénicillamyl)-L-valine.

30. Composé selon la revendication 1, qui est la N-(N-L-γ-glutamyl-L-pénicillamyl)-phénylalanine.

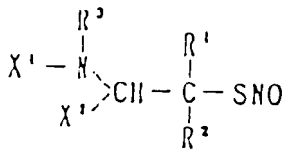
31. Composé selon la revendication 1, qui est l'acide N-(N-L-γ-glutamyl-L-pénicillamyl)-L-glutamique.

32. Composé selon la revendication 1, qui est la N-(N-L-γ-glutamyl-D-pénicillamyl)diphénylméthylamine.

33. Composition pharmaceutique propre au traitement curatif ou prophylactique de l'hypertension ou de l'angine de poitrine, qui comprend (a) comme substance active, une quantité efficace d'un composé selon la revendication 1 ou d'un sel de celui-ci et (b) une matière de support, un excipient ou un diluant pharmaceutiquement acceptable pour ce composé.

34. Utilisation d'un composé selon la revendication 1 ou d'un sel de celui-ci pour la préparation d'un médicament pour le traitement thérapeutique d'un mammifère.

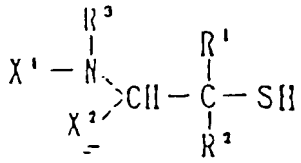
35. Procédé de préparation d'un composé de formule (I):



dans laquelle R^1 et R^2 sont, indépendamment l'un de l'autre, un atome d'hydrogène ou un radical hydrocarboné qui peut être substitué; R^3 est un atome d'hydrogène, un groupe acyle ou un radical hydrocarboné qui peut être substitué; X^1 est un atome d'hydrogène, un groupe acyle, un groupe alcoxy inférieur ou un radical hydrocarboné qui peut être substitué; X^2 est un groupe acyle ou un groupe carboxylique qui peut être estérifié ou qui peut former un amide; avec la condition que X^1 n'est pas un atome d'hydrogène ou

le groupe acétyle lorsque X^2 est un groupe carboxylique et que X^1 n'est pas un groupe acétyle ou un groupe γ-glutamyle lorsque R^1 et R^2 sont tous deux des atomes d'hydrogène, ou d'un sel de celui-ci, selon lequel

(a) on soumet un composé de formule (II):

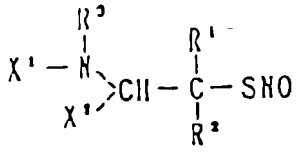


dans laquelle R^1, R^2, R^3, X^1 et X^2 sont tels que défini ci-dessus, à une réaction de nitrosation et, si désiré,

(b) on transforme le produit obtenu par le procédé (a) ci-dessus en un sel de celui-ci.

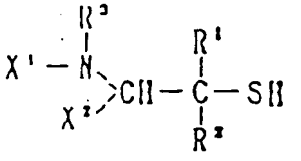
Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'un composé de formule (I):



dans laquelle R^1 et R^2 sont, indépendamment l'un de l'autre, un atome d'hydrogène ou un radical hydrocarboné qui peut être substitué; R^3 est un atome d'hydrogène, un groupe acyle ou un radical hydrocarboné qui peut être substitué; X^1 est un atome d'hydrogène, un groupe acyle, un groupe alcoxy inférieur ou un radical hydrocarboné qui peut être substitué; X^2 est un groupe acyle ou un groupe carboxylique qui peut être estérifié ou qui peut former un amide; avec la condition que X^1 n'est pas un atome d'hydrogène ou le groupe acétyle lorsque X^2 est un groupe carboxylique et que X^1 n'est pas un groupe acétyle ou un groupe γ-glutamyle lorsque R^1 et R^2 sont tous deux des atomes d'hydrogène, ou d'un sel de celui-ci, selon lequel

(a) on soumet un composé de formule (II):



dans laquelle R^1, R^2, R^3, X^1 et X^2 sont tels que défini ci-dessus, à une réaction de nitrosation et, si désiré,

(b) on transforme le produit obtenu par le procédé (a) ci-dessus en un sel de celui-ci.

2. Procédé selon la revendication 1, dans lequel R^1 et R^2 sont, indépendamment l'un de l'autre, un radical hydrocarboné qui peut être substitué ou R^1 et R^2 peuvent être liés l'un à l'autre pour former un cycle de formule: $-(CH_2)_n-$ dans laquelle n est un nombre entier de 2 à 6.

3. Procédé selon la revendication 1, dans lequel X^1 est un acyle dérivé d'un acide aminé.

4. Procédé selon la revendication 1, dans lequel R^1 et R^2 sont, indépendamment l'un de l'autre, un radical hydrocarboné qui peut être substitué; R^3 est un atome d'hydrogène, un groupe acyle ou un radical hydrocarboné qui peut être substitué; X^1 est un acyle dérivé d'un acide aminé; X^2 est un groupe acyle ou un groupe carboxylique qui peut être estérifié ou qui peut former un amide.

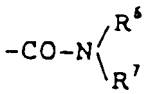
5. Procédé selon la revendication 1, dans lequel le radical hydrocarboné représenté par R^1, R^2, R^3 ou X^1 est un radical hydrocarboné à chaîne saturée, à chaîne insaturée, un radical hydrocarboné cyclique saturé ou cyclique insaturé, dont chacun peut être substitué par un à trois groupes choisis dans le groupe consistant en un atome d'halogène, un groupe nitro, nitrile, hydroxyle, carboxylique, alcoxy en C_{1-4}, alcoylthio en C_{1-4}, amino, mono ou di(alcoyle en C_{1-4})amino, mono ou di-aralcolyamino, mono ou di-pyridylamino, alcoxy en C_{1-4}-carbonyle, cycloalcoyle en C_{3-6}-carbonyle, carbamoyle, mono ou di(alcoyle en C_{1-4})carbamoyle et un groupe phényle, phénoxy, benzoyle, phénoxycarbonyle, phénylalcoyle en C_{1-4}-carbamoyle ou phénylcarbamoyle, dans lesquels chacun desdits groupes phényle peut être substitué par 1 à 4 groupes choisis dans le groupe consistant en un alcoyle en C_{1-4}, un atome d'halogène, un groupe hydroxyle, benzyloxy, amino, mono ou di(alcoyle en C_{1-4})amino, nitro et alcoxy en C_{1-4}-carbonyle.

6. Procédé selon la revendication 1, dans lequel le groupe acyle représenté par R^3, X^1 ou X^2 est un groupe acyle carboxylique, carbamique, sulfonique ou oxycarboxylique dont chacun peut être substitué par 1 à 3 groupes choisis dans le groupe consistant en un atome d'halogène, un groupe nitro, nitrile, hydroxyle, carboxylique, alcoxy en C_{1-4}, alcoylthio en C_{1-4}, amino, mono ou di(alcoyle en C_{1-4})amino, mono ou di-aralcoylamino, mono ou di-pyridylcarbonylamino, alcoyle en C_{1-6}-carbonyle, alcoxy en C_{1-4}-carbonyle, cycloalcoyle en C_{3-6}-carbonyle, carbamoyle, mono ou di(alcoyle en C_{1-4})-carbamoyle et un groupe phényle, phénoxy, benzoyle, phénoxycarbonyle, phényl-alcoyle en C_{1-4}-carbamoyle ou phénylcarbamoyle dans lesquels chacun desdits groupes phényle peut être substitué par 1 à 4 groupes choisis dans le groupe consistant en un alcoyle en C_{1-4}, un atome d'halogène, un groupe hydroxyle, benzyloxy, amino, mono ou di(alcoyle en C_{1-4})amino, nitro et alcoxy en C_{1-4}-carbonyle.

7. Procédé selon la revendication 1, dans lequel le groupe alcoxy inférieur est un groupe alcoxy en C_{1-6}.

8. Procédé selon la revendication 1, dans lequel le groupe carboxylique qui peut être estérifié est un carboxyle ou un groupe de formule: $-CO-OR^5$, dans laquelle R^5 est un radical hydrocarboné qui peut être substitué.

9. Procédé selon la revendication 1, dans lequel le groupe carboxylique qui peut former un amide est un carboxyle ou un groupe de formule:



dans laquelle R^6 est un atome d'hydrogène ou un radical hydrocarboné qui peut être substitué et R^7 est un atome d'hydrogène ou un groupe alcoyle inférieur ou R^6 et R^7 forment ensemble avec l'atome d'azote adjacent un groupe amino cyclique.

10. Procédé selon la revendication 1, dans lequel R^1 et R^2 sont, indépendamment l'un de l'autre, un radical hydrocarboné à chaîne saturée ou cyclique insaturée ou R^1 et R^2 forment ensemble avec l'atome de carbone adjacent un groupe cyclopentyle ou cyclohexyle.

11. Procédé selon la revendication 1, dans lequel R^1 et R^2 sont, indépendamment l'un de l'autre, un groupe alcoyle en C_{1-6}.

12. Procédé selon la revendication 1, dans lequel R^1 et R^2 sont un méthyle.

13. Procédé selon la revendication 1, dans lequel R^3 est un atome d'hydrogène ou un groupe acyle.

14. Procédé selon la revendication 13, dans lequel le groupe acyle est un alcoyle en C_{1-6}-carbonyle ou un aryle en C_{6-10}-carbonyle.

15. Procédé selon la revendication 1, dans lequel R^3 est un atome d'hydrogène.

16. Procédé selon la revendication 1, dans lequel X^1 est un atome d'hydrogène ou un groupe acyle.

17. Procédé selon la revendication 13, dans lequel le groupe acyle est un groupe acyle dérivé d'un acide aminé.

18. Procédé selon la revendication 17, dans lequel l'acide aminé est la glycine, l'alanine, l'acide glutamique, la leucine, l'isoleucine, la phénylalanine, l'acide aspartique, la cystéine, la sarcosine, la glutamine, l'asparagine ou la proline.

19. Procédé selon la revendication 17, dans lequel l'acide aminé est la glycine, l'acide aspartique, l'asparagine, l'acide glutamique, la glutamine ou la phénylalanine.

20. Procédé selon la revendication 17, dans lequel l'acide aminé est l'acide glutamique ou l'acide aspartique.

21. Procédé selon la revendication 1, dans lequel X^2 est un groupe carboxylique qui peut être estérifié.

22. Procédé selon la revendication 1, dans lequel X^2 est un groupe acyle carboxylique ou carbamique.

23. Procédé selon la revendication 22, dans lequel le groupe acyle carbamique est un groupe aminocarbonyle ou un groupe carboxylique formant un amide avec un acide aminé.

24. Procédé selon la revendication 23, dans lequel l'acide aminé est la glycine, l'alanine, l'acide glutamique, la leucine, l'isoleucine, la phénylalanine, l'acide aspartique, la cystéine, la sarcosine, la glutamine, l'asparagine ou la proline.

25. Procédé selon la revendication 23, dans lequel l'acide aminé est la glycine, l'acide aspartique, l'asparagine, la phénylalanine, l'acide glutamique ou la glutamine.

26. Procédé selon la revendication 1, dans lequel R^1 et R^2 sont, indépendamment l'un de l'autre, un groupe alcoyle en C_{1-6}, phényle ou naphtyle ou R^1 et R^2 forment ensemble avec l'atome de carbone adjacent un groupe cyclopentyle ou cyclohexyle; R^3 est un atome d'hydrogène ou un groupe acyle aromatique en C_{6-10}; X^1 est un atome d'hydrogène ou un groupe acyle dérivé d'un acide aminé dans lequel ledit acide aminé est choisi dans le groupe consistant en la glycine, l'acide aspartique, la phénylalanine, l'asparagine, l'acide gluta. mique et la glutamine; X^2 est un groupe carboxylique, aminocarbonyle ou un groupe carboxylique formant un amide avec un radical d'acide aminé dans lequel ledit acide aminé est choisi dans le groupe consistant en la glycine, l'acide aspartique, la phénylalanine, l'asparagine, l'acide glutamique et la glutamine.

27. Procédé selon la revendication 1, dans lequel le sel est un sel pharmaceutiquement acceptable.

28. Procédé selon la revendication 1, qui est la N-(N-L-γ-glutamyl-D-pénicillamyl)glycine.

29. Procédé selon la revendication 1, dans lequel ledit composé (I) est la N-(N-L-γ-glutamyl-L-pénicillamyl)-L-valine.

30. Procédé selon la revendication 1, dans lequel ledit composé (I) est la N-(N-L-γ-glutamyl-L-pénicillamyl)-L-phénylalanine.

31. Procédé selon la revendication 1, dans lequel ledit composé (I) est l'acide N-(N-L-γ-glutamyl-L-pénicillamyl)-L-glutamique.

32. Procédé selon la revendication 1, dans lequel ledit composé (I) est la N-(N-L-γ-glutamyl-D-pénicillamyl)diphénylméthylamine.

33. Composition pharmaceutique propre à être utilisée dans la préparation d'un médicament approprié au traitement curatif ou prophylactique de l'hypertension ou de l'angine de poitrine, qui comprend (a) comme substance active, une quantité efficace d'un composé selon la revendication 1 ou d'un sel de celui-ci et (b) une matière de support, un excipient ou un diluant pharmaceutiquement acceptable pour ce composé.

34. Utilisation d'un composé selon la revendication 1 ou d'un sel de celui-ci pour la préparation d'un médicament pour le traitement thérapeutique d'un mammifère.